Mohamed, A.
09/926679

(FILE 'REGISTRY' ENTERED AT 14:43:28 ON 22 OCT 2003)

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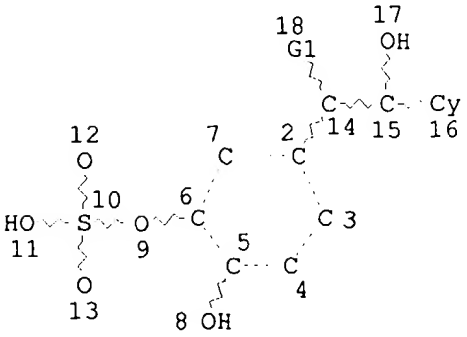

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STEREO ATTRIBUTES: NONE
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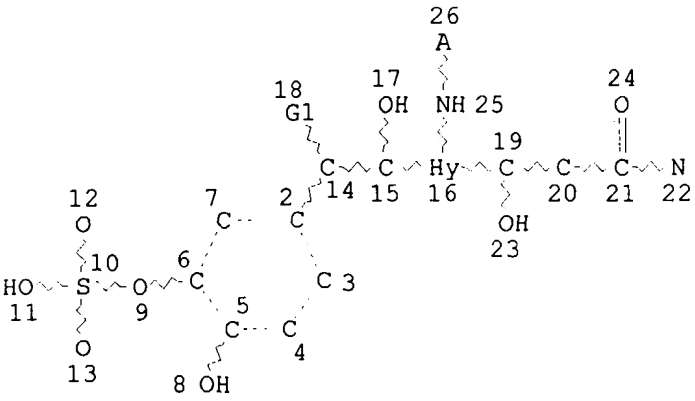

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STEREO ATTRIBUTES: NONE

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SEARCH TIME: 00.00.01

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                N B)/CN
                E ER 30346/CN 5
L7            1 SEA ABB=ON  PLU=ON  "ER 30346"/CN
                E SCH 56592/CN 5
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L9            4 SEA ABB=ON  PLU=ON  (NYSTATIN OR FLUCYTOSINE OR NIKKOMYCI
                N X OR PREDAMYCIN)/CN
L10           1 SEA ABB=ON  PLU=ON  SORDARIN/CN
L11          14 SEA ABB=ON  PLU=ON  L6 OR L7 OR L8 OR L9 OR L10

     FILE 'HCAPLUS' ENTERED AT 14:52:47 ON 22 OCT 2003
L12          84 S L5
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                E OR ER30346 OR ER 30346 OR SCH56592 OR SCH 56592 OR
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                X OR PREDAMYCIN OR SORDARIN OR LIPOSOM## OR LIPID)

E1 THROUGH E19 ASSIGNED

L13  ANSWER 1 OF 30  HCAPLUS  COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER:         2003:757023  HCAPLUS
TITLE:                    Bioadhesive vaginal drug delivery system
                          containing an acidic buffer
INVENTOR(S):              Kirschner, Mitchell I.; Levinson, R. Saul;
                          Riley, Thomas C.; Hermelin, Marc S.
PATENT ASSIGNEE(S):       USA
SOURCE:                   U.S. Pat. Appl. Publ., 13 pp.
                          CODEN: USXXCO
DOCUMENT TYPE:            Patent
LANGUAGE:                 English
FAMILY ACC. NUM. COUNT:   1
PATENT INFORMATION:

     PATENT NO.        KIND  DATE          APPLICATION NO.  DATE
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     US 2003180366      A1   20030925      US 2002-101014   20020320
     CN 1444926         A    20031001      CN 2002-127087   20020729
     JP 2003286193      A2   20031007      JP 2002-266381   20020912
     FR 2837389         A1   20030926      FR 2002-14858    20021127
     WO 2003079981      A2   20031002      WO 2003-US8266   20030319
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             GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ,
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             NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ,
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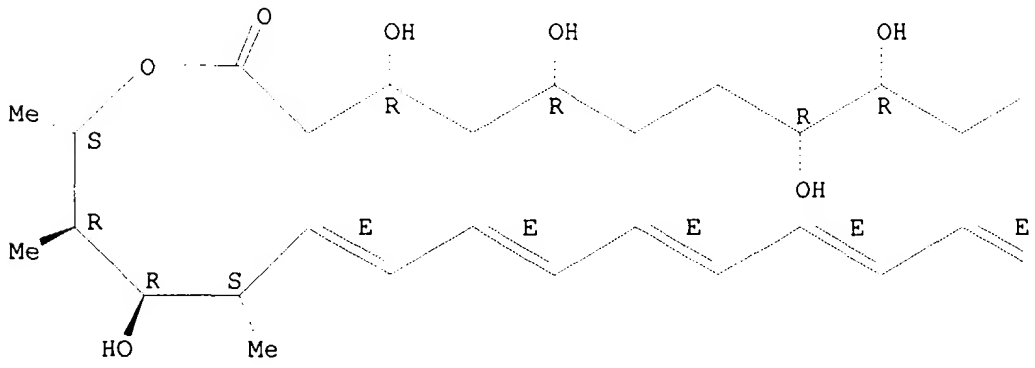
GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: US 2002-101014 A 20020320

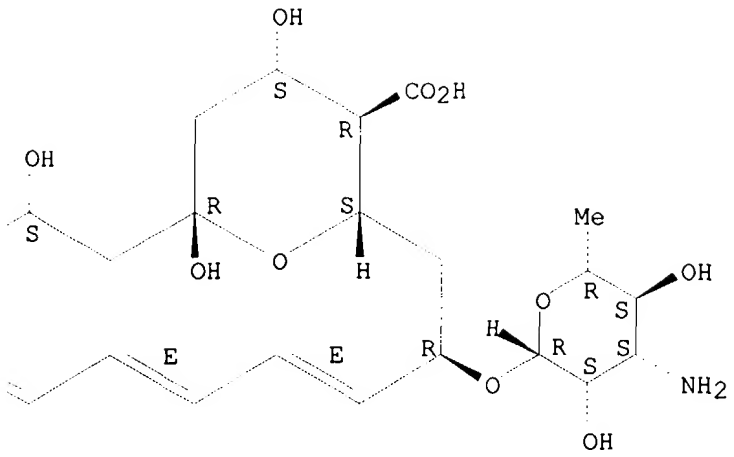
AB The present invention relates to a novel essentially pH neutral vaginal drug delivery system suitable for modified delivery of a therapeutically active material in the vaginal cavity. The vaginal drug delivery system comprises an essentially pH neutral emulsion having globules having two phases, an internal water soluble phase and an external water-insol. phase or film, wherein the water-soluble interior phase contains a therapeutically active drug or drugs. One novel aspect of the vaginal drug delivery system is that the internal water soluble phase comprises an acidic buffered phase. For example, a vaginal drug delivery system was prepared containing metronidazole 0.75%, water 24.676%, glycerin 47.25%, acetic acid 0.225%, sodium acetate 0.20%, sodium chloride 0.75%, methylparaben 0.09%, propylparaben 0.035%, butylparaben 0.024%, sucrose 8.0%, mineral oil 13.0%, and polyethylene glycol (30) dipolyhydroxystearate 5.0%.

IT **1397-89-3, Amphotericin B**
1400-61-9, Nystatin 22916-47-8,
Miconazole 84625-61-6, Itraconazole
86386-73-4, Fluconazole 137234-62-9,
Voriconazole 171228-49-2, Posaconazole
235114-32-6, Micafungin
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bioadhesive vaginal drug delivery system containing acidic buffer)

RN 1397-89-3 HCAPLUS
CN Amphotericin B (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.





RN 1400-61-9 HCAPLUS
CN Nystatin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
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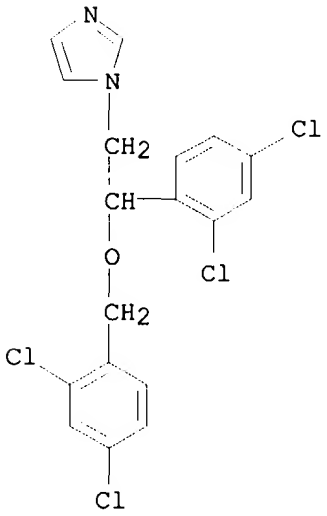
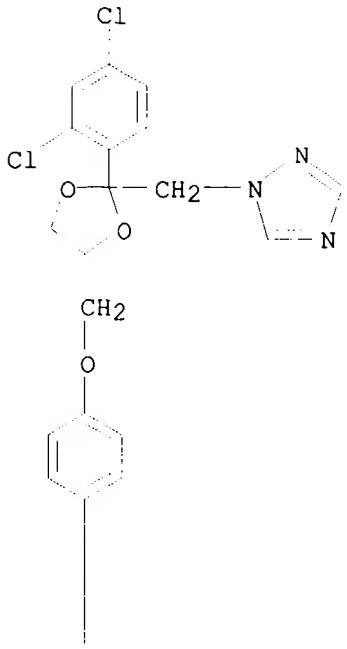


RN 84625-61-6 HCAPLUS
CN 3H-1,2,4-Triazol-3-one, 4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)- (9CI) (CA INDEX NAME)

PAGE 1-A



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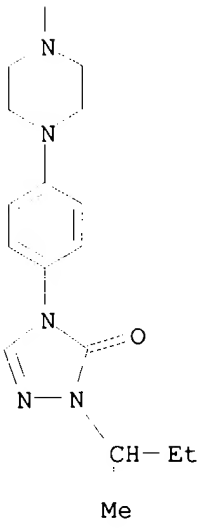
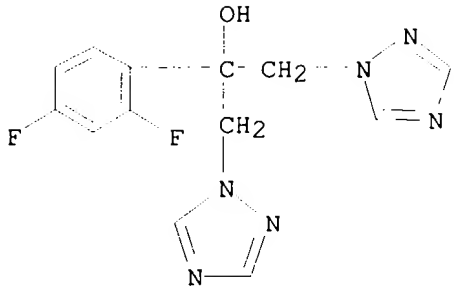
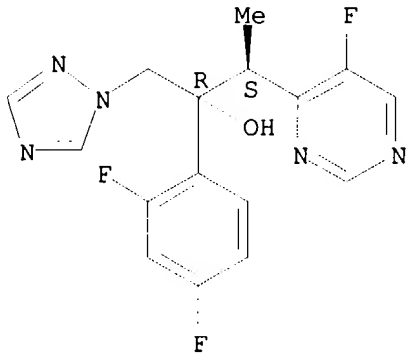


RN 86386-73-4 HCAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)- (9CI) (CA INDEX NAME)



RN 137234-62-9 HCAPLUS
CN 4-Pyrimidineethanol, α-(2,4-difluorophenyl)-5-fluoro-β-methyl-α-(1H-1,2,4-triazol-1-ylmethyl)-, (αR,βS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 171228-49-2 HCAPLUS
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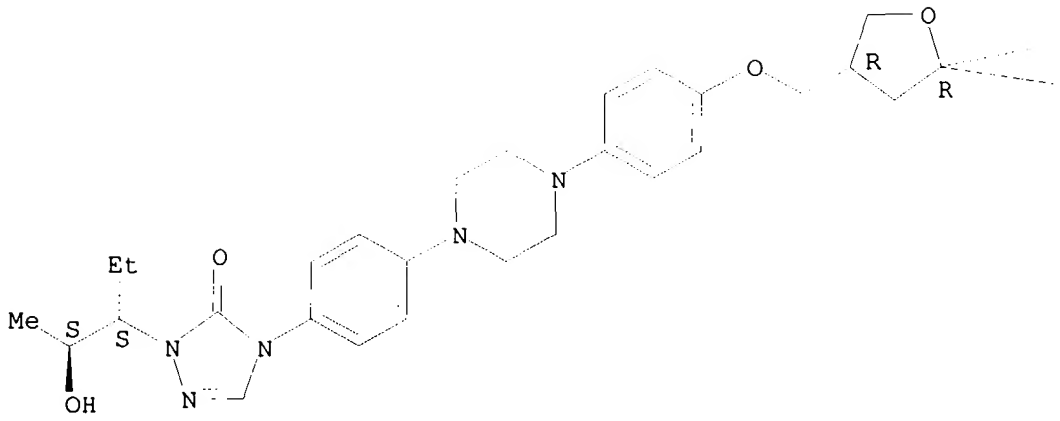
Absolute stereochemistry. Rotation (-).

PAGE 1-A



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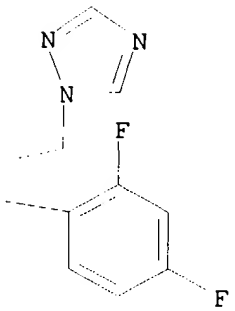

RN 235114-32-6 HCAPLUS
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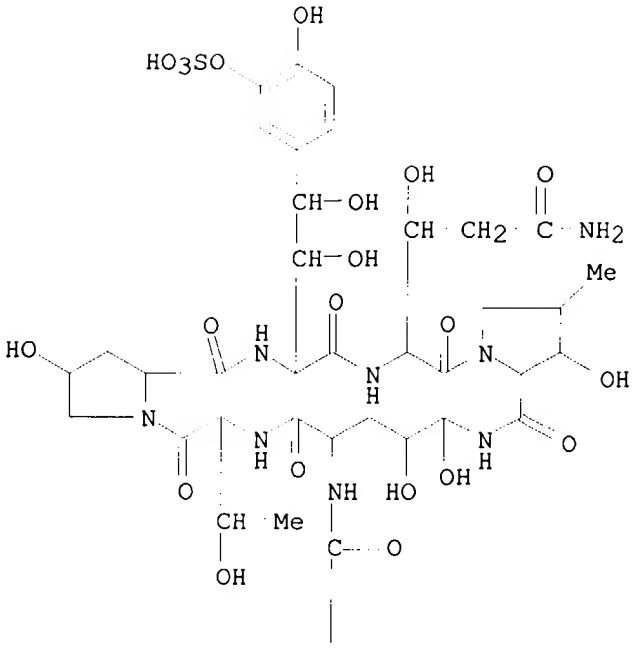
PAGE 1-A



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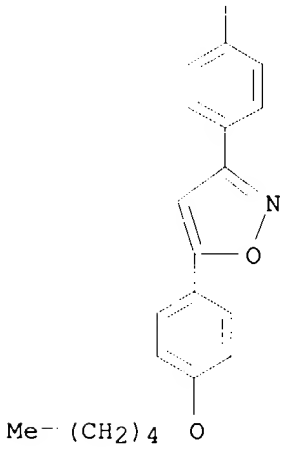


L13 ANSWER 2 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:280528 HCAPLUS
DOCUMENT NUMBER: 139:127475
TITLE: Efficacy of micafungin alone or in combination against systemic murine aspergillosis
AUTHOR(S): Luque, Javier Capilla; Clemons, Karl V.; Stevens, David A.

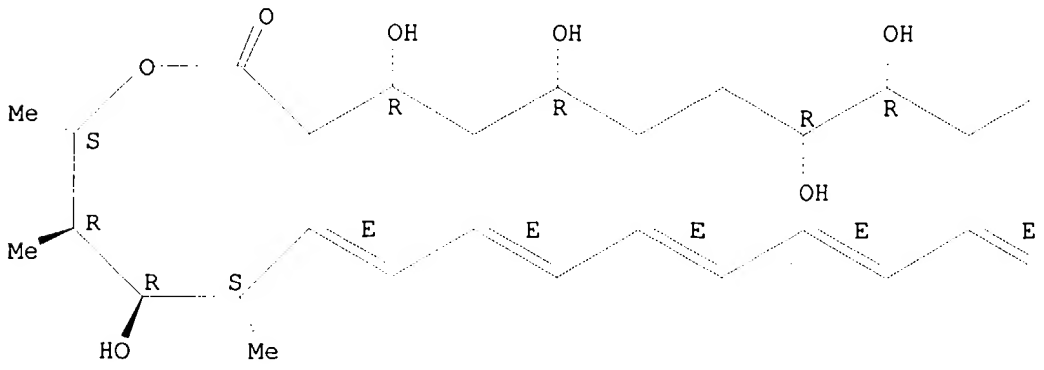
CORPORATE SOURCE: University of Rovira i Virgili, Reus, Spain
SOURCE: Antimicrobial Agents and Chemotherapy (2003), 47(4), 1452-1455
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We tested the efficacy of micafungin (FK) alone or in combination with other antifungals against systemic murine aspergillosis. FK alone at 10 mg/kg of body weight/dose prolonged survival ($P = 0.01$) and reduced CFU in the brain and kidney. Combination therapy that used suboptimal FK with **amphotericin B** or **itraconazole** prolonged survival. Although no survivors were free of infection, no antagonism was seen. Nikkomycin Z with FK showed significantly greater potency ($P < 0.01$) than either alone.

IT **1397-89-3, Amphotericin B**
84625-61-6, Itraconazole 235114-32-6,
Micafungin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(micafungin alone or in combination against systemic murine aspergillosis)

RN 1397-89-3 HCAPLUS
CN Amphotericin B (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.



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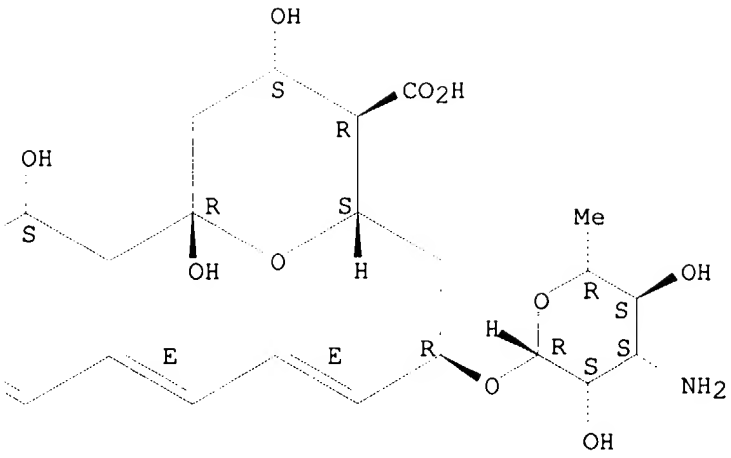
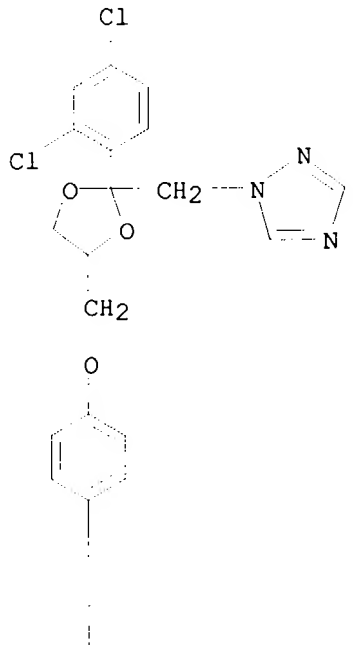


RN 84625-61-6 HCAPLUS
CN 3H-1,2,4-Triazol-3-one, 4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)- (9CI) (CA INDEX NAME)

PAGE 1-A



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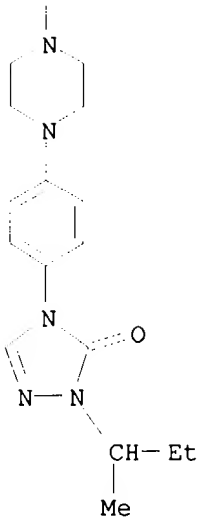
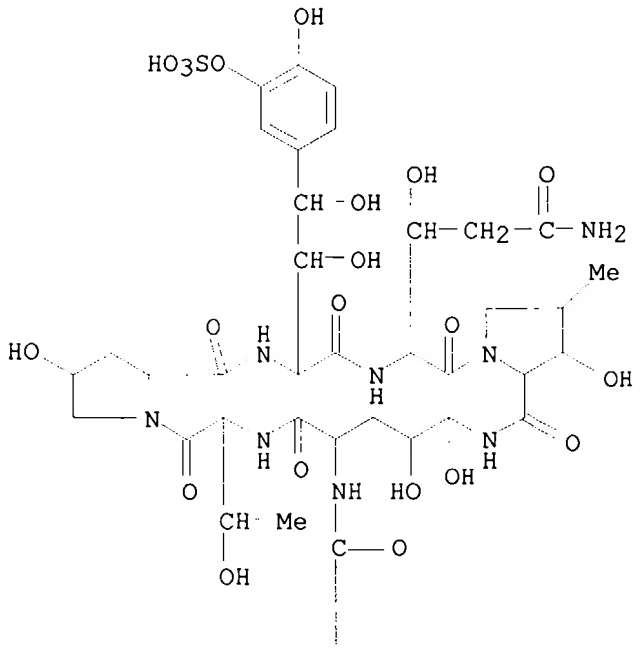
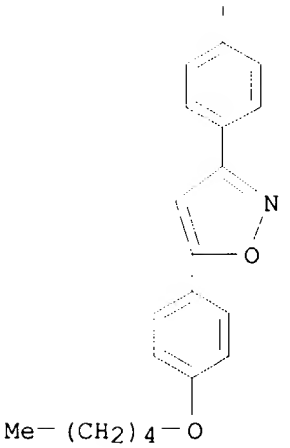


RN 235114-32-6 HCAPLUS
CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]- (9CI) (CA INDEX NAME)

PAGE 1-A





REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 3 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:280509 HCAPLUS
DOCUMENT NUMBER: 139:19484
TITLE: In vitro antifungal activity of micafungin (FK463) against dimorphic fungi: Comparison of yeast-like and mycelial forms
AUTHOR(S): Nakai, Toru; Uno, Jun; Ikeda, Fumiaki; Tawara, Shuichi; Nishimura, Kazuko; Miyaji, Makoto
CORPORATE SOURCE: Research Center for Pathogenic Fungi and Microbial Toxicoses, Chiba University, Chiba, 260-8673, Japan
SOURCE: Antimicrobial Agents and Chemotherapy (2003), 47(4), 1376-1381
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The characteristics of in vitro micafungin (FK463) antifungal activity against six species of dimorphic fungi were investigated in accordance with the NCCLS M27-A microdilution methods. MICs of micafungin, **amphotericin B**, **itraconazole**, and **fluconazole** for Histoplasma capsulatum var. capsulatum, Blastomyces dermatitidis, Paracoccidioides brasiliensis, Penicillium marneffei, and Sporothrix schenckii were determined both for the yeast-like form and mycelial form. Coccidioides immitis was tested only in its mycelial form. We have clearly demonstrated that the in vitro activity of micafungin depends considerably on the growth form of dimorphic fungi. Micafungin exhibited potent activity against the mycelial forms of H. capsulatum, B. dermatitidis, and C. immitis (MIC range, 0.0078 to 0.0625 μg/mL), while it was very weakly active against their yeast-like forms (MIC range, 32 to >64 μg/mL). Micafungin was also more active against the mycelial forms than the yeast-like forms of Paracoccidioides brasiliensis, Penicillium marneffei, and S. schenckii. The MICs of

amphotericin B were 2 to 5 dilns. lower for the mycelial forms than for the yeast-like forms of B. dermatitidis and Paracoccidioides brasiliensis. There was no apparent difference in the activity of **itraconazole** between the two forms. The MICs of **fluconazole** for the yeast-like forms were generally lower than those for the mycelial forms, and considerably so for B. dermatitidis. These results suggest that the growth form employed in antifungal susceptibility testing of dimorphic fungi can considerably influence the interpretation of results. At present, it cannot be judged whether micafungin has clin. usefulness for dimorphic fungus infections, since for most fungi it remains uncertain which growth form correlates better with therapeutic outcome. However, the results of this study warrant further investigations of micafungin as a therapeutic agent for infections caused by dimorphic fungi.

IT **235114-32-6**, Micafungin
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vitro antifungal activity of micafungin (FK463) against dimorphic fungi yeast-like and mycelial forms)

RN 235114-32-6 HCAPLUS

CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]- (9CI) (CA INDEX NAME)

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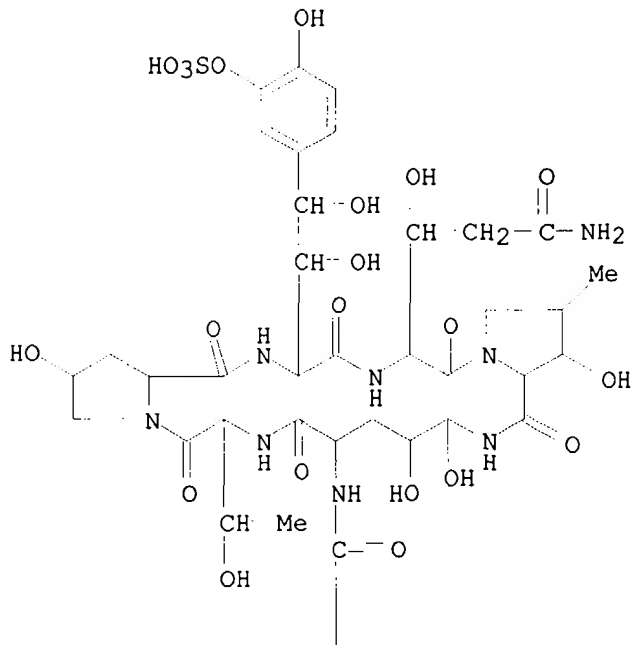

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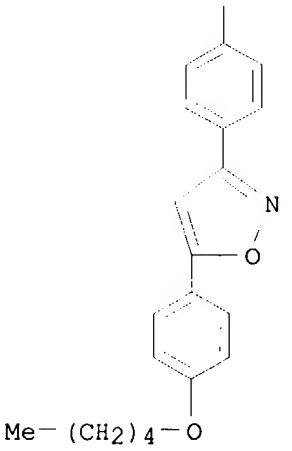
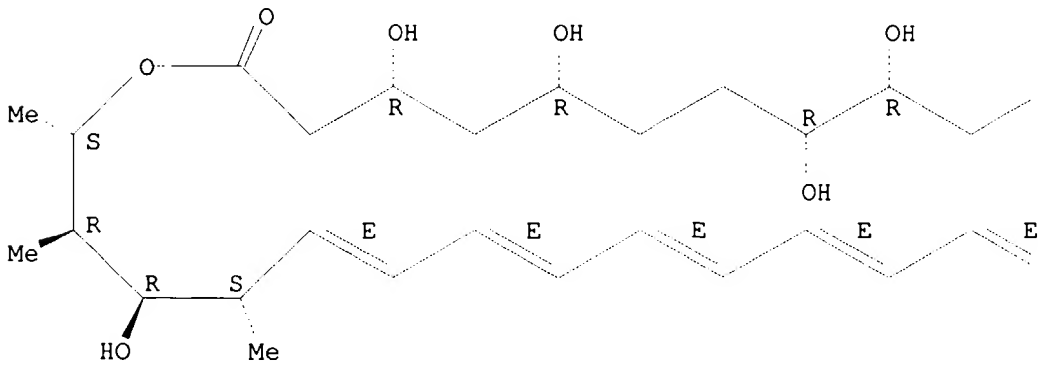


IT **1397-89-3, Amphotericin B**
84625-61-6, Itraconazole 86386-73-4,
Fluconazole
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vitro antifungal activity of micafungin (FK463) against dimorphic fungi yeast-like and mycelial forms comparison to)
RN 1397-89-3 HCAPLUS
CN Amphotericin B (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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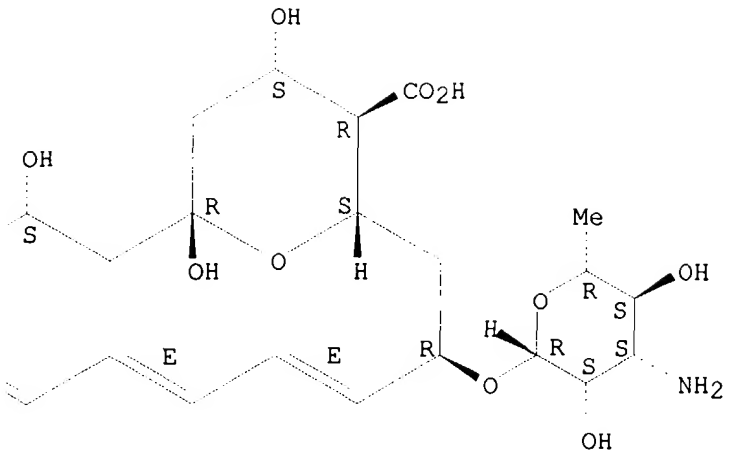

RN 84625-61-6 HCAPLUS
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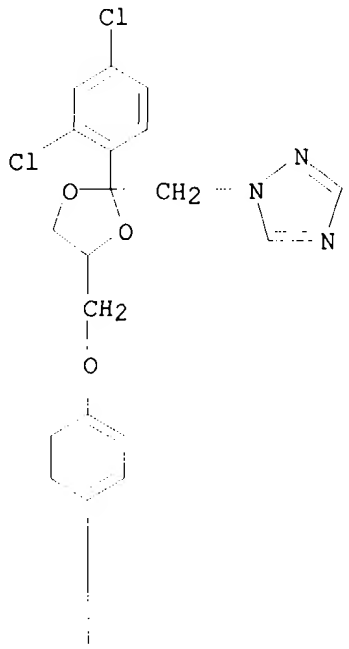
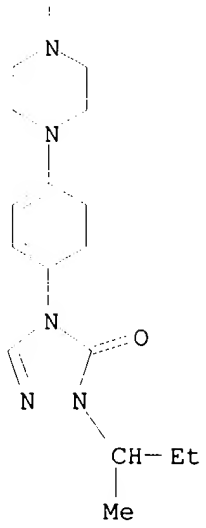
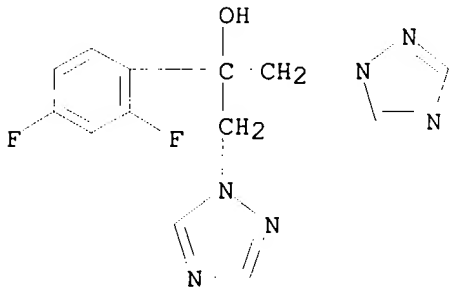
PAGE 1-A





RN 86386-73-4 HCAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 4 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:273734 HCAPLUS
DOCUMENT NUMBER: 139:143421
TITLE: Activity of micafungin (FK463) against an **itraconazole**-resistant strain of Aspergillus fumigatus and a strain of Aspergillus terreus demonstrating in vivo resistance to **amphotericin B**
AUTHOR(S): Warn, P. A.; Morrissey, G.; Morrissey, J.; Denning, D. W.
CORPORATE SOURCE: School of Medicine, Hope Hospital, University of Manchester, Manchester, M6 8HD, UK
SOURCE: Journal of Antimicrobial Chemotherapy (2003), 51(4), 913-919
CODEN: JACHDX; ISSN: 0305-7453

PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

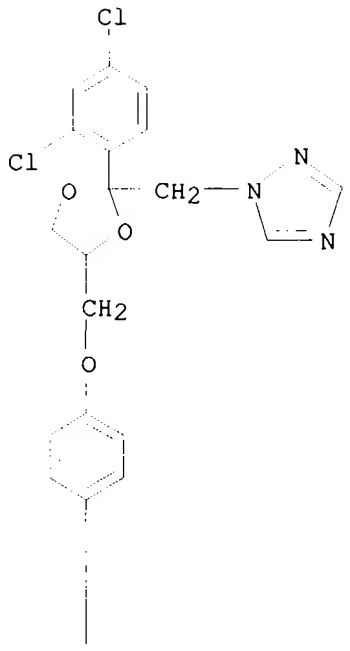
AB We compared the activity of four doses of micafungin (FK463) with that of **amphotericin B, liposomal amphotericin B** and **itraconazole** in a murine model of disseminated aspergillosis. Temporarily neutropenic mice were infected with a LD of either an **itraconazole**-resistant Aspergillus fumigatus isolate or Aspergillus terreus, a species that is less susceptible to **amphotericin B**. Treatment was started 24 h after infection and lasted for 7 days. Mice were treated with either **amphotericin B** (0.5 or 5 mg/kg), **liposomal** amphotericin (5 or 25 mg/kg), **itraconazole** (25 or 75 mg/kg) or FK463 (either 1, 2, 5 or 10 mg/kg). Treatment of the A. fumigatus model with either **amphotericin B, liposomal** amphotericin or FK463 prolonged survival. Doses of FK463 5 and 10 mg/kg had a 100% survival. Treatment of A. terreus infection with either **itraconazole** or FK463, but not **amphotericin B**, also prolonged survival. Doses of **liposomal** amphotericin of 5 and 25 mg/kg were ineffective against A. terreus infection. No treatment regime was able to totally clear the liver or kidneys in either model. The data indicate that FK463 may have a clin. role in the treatment of life-threatening invasive aspergillosis.

IT **84625-61-6, Itraconazole 235114-32-6,** Micafungin
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(activity of micafungin against Aspergillus)

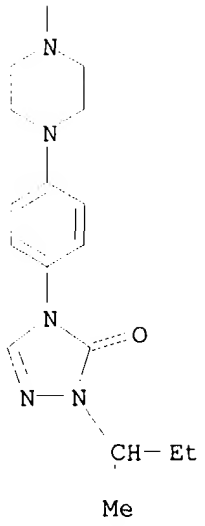
RN 84625-61-6 HCAPLUS

CN 3H-1,2,4-Triazol-3-one, 4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)- (9CI) (CA INDEX NAME)

PAGE 1-A

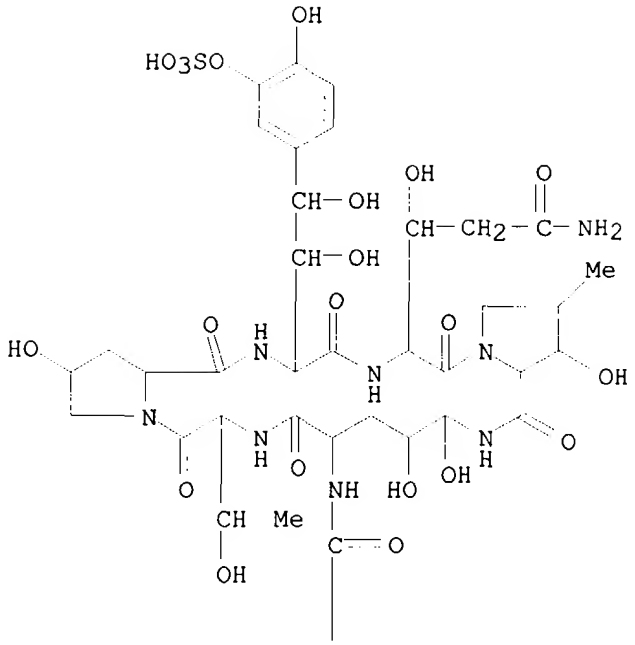


PAGE 2-A



RN 235114-32-6 HCAPLUS
CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]- (9CI) (CA INDEX NAME)

PAGE 1-A



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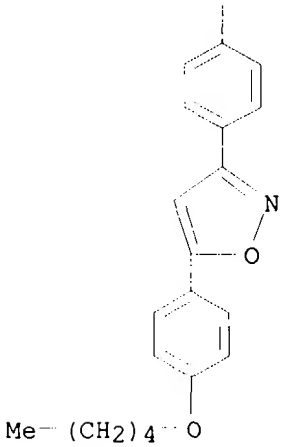
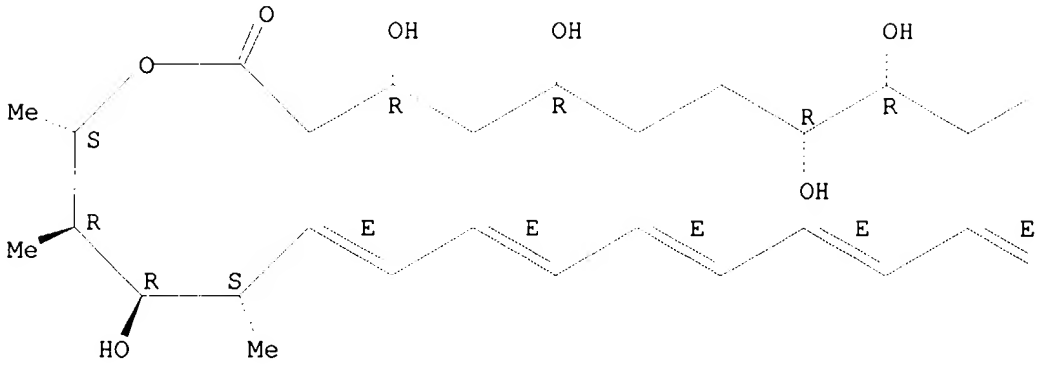


IT **1397-89-3, Amphotericin B**
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(and **liposomal**; activity of micafungin against Aspergillus)
RN 1397-89-3 HCAPLUS
CN Amphotericin B (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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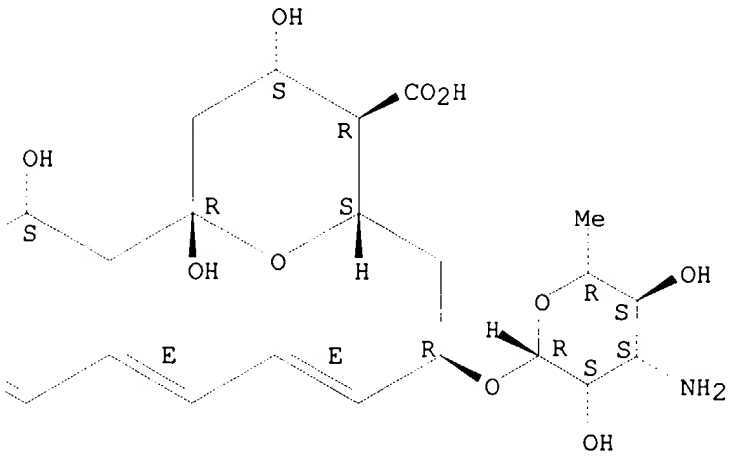

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 5 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:6324 HCAPLUS
DOCUMENT NUMBER: 139:17114
TITLE: Drug interactions of micafungin in vitro
AUTHOR(S): Kaneko, Hayato; Yamato, Yasuhiro; Hashimoto, Tomoko; Ishii, Ikuko; Shiraga, Toshifumi;

Kawamura, Akio; Terakawa, Masato; Kagayama, Akira
CORPORATE SOURCE: Biopharmaceutical and Pharmacokinetic Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., Osaka, 532-8514, Japan
SOURCE: Nippon Kagaku Ryoho Gakkai Zasshi (2002), 50(Suppl. 1), 94-103
CODEN: NKRZE5; ISSN: 1340-7007
PUBLISHER: Nippon Kagaku Ryoho Gakkai
DOCUMENT TYPE: Journal
LANGUAGE: Japanese
AB The in vitro drug interactions of micafungin (MCFG), a new echinocandin-like lipopeptide antifungal agent, were evaluated using human serum and human liver microsomes. 1. The percent of MCFG bound to human serum proteins was as high as 99.74%. Warfarin, diazepam, salicylic acid, and methotrexate did not affect the protein binding of MCFG. 2. Based on the results at the concns. ranging from 0.1 to 1 mmol/L (130-1300 μg/mL) of MCFG, the binding constant (KD) of MCFG at the bilirubin binding site was calculated to be 2.0 + 103 L/mol, indicating that MCFG has a lower affinity to the bilirubin binding site than salicylic acid (5.0 + 103 L/mol) or sulfisoxazole (1.4 + 104 L/mol). 3. M5 and M13 formation activities significantly correlated with the activities of coumarin 7-hydroxylase and testosterone 6β-hydroxylase. M13 formation activity also significantly correlated with the activities of tolbutamide methyl-hydroxylase and S-mephenytoin 4'-hydroxylase. 4. The metabolism of MCFG was inhibited by tranylcypromine and **ketoconazole** (KCZ). The 50% inhibitory concentration (IC50) of cyclosporin A, tacrolimus, and KCZ for the metabolic activity of MCFG was >100, >100 and 6.2 μmol/L, resp. 5. The IC50 of MCFG, **fluconazole** (FLCZ) and KCZ for the metabolic activity of terfenadine was 67.7, >100 and 0.46 μmol/L, resp., and 24.9, 0.12 and 44.2 μmol/L for astemizole. The inhibition constant of MCFG, FLCZ, and KCZ for the metabolic activity of nifedipine was 17.3, 0.012 and 10.7 μmol/L, resp. 6. The IC50 of MCFG, caspofungin acetate and KCZ for the metabolic activity of cyclosporin A was 31, 39 and 0.14 μmol/L, resp.
IT **539826-01-2**
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(M5, hydroxyl form at side chain; drug interactions of micafungin in vitro)
RN 539826-01-2 HCAPLUS
CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-[[(4S)-4-hydroxypentyl]oxy]phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]- (9CI) (CA INDEX NAME)

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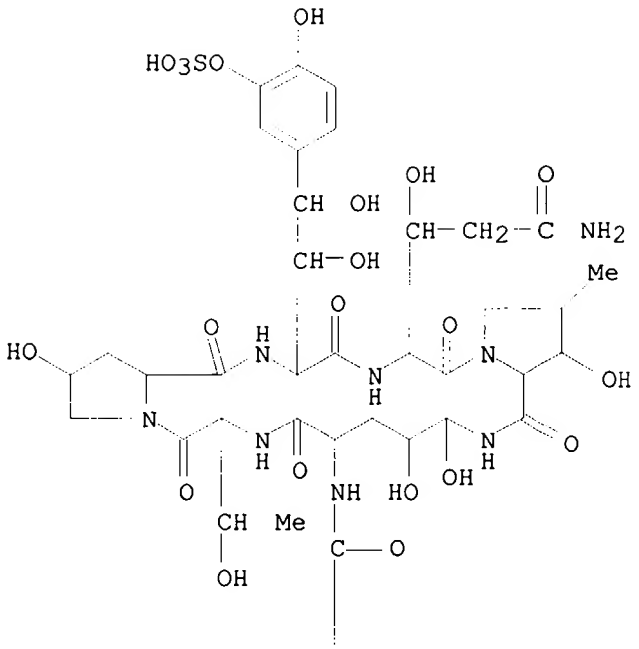

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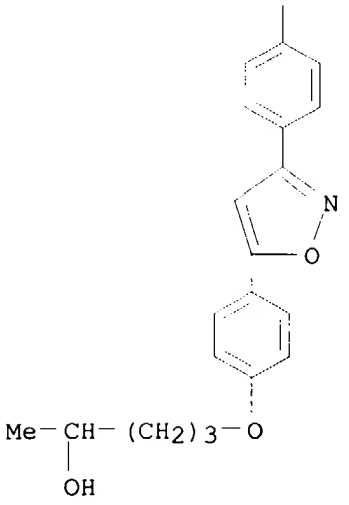
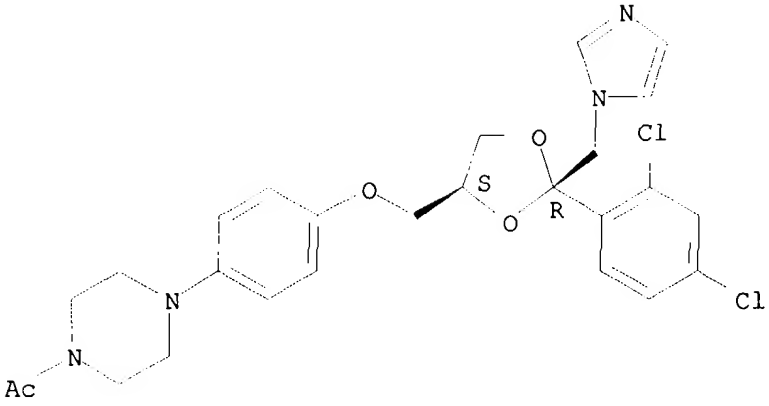


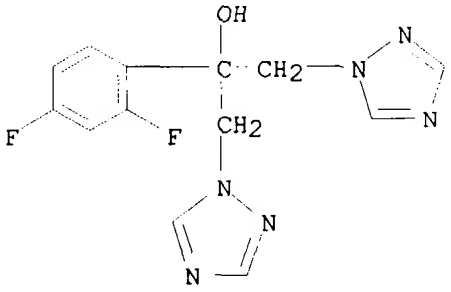
IT **65277-42-1, Ketoconazole 86386-73-4, Fluconazole**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (drug interactions of micafungin in vitro)
RN 65277-42-1 HCAPLUS
CN Piperazine, 1-acetyl-4-[4-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-

imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.



RN 86386-73-4 HCAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)- (9CI) (CA INDEX NAME)



IT **235114-32-6**, Micafungin
RL: BSU (Biological study, unclassified); PKT (Pharmacokinetics); BIOL (Biological study)
(drug interactions of micafungin in vitro)
RN 235114-32-6 HCAPLUS
CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]- (9CI) (CA INDEX NAME)

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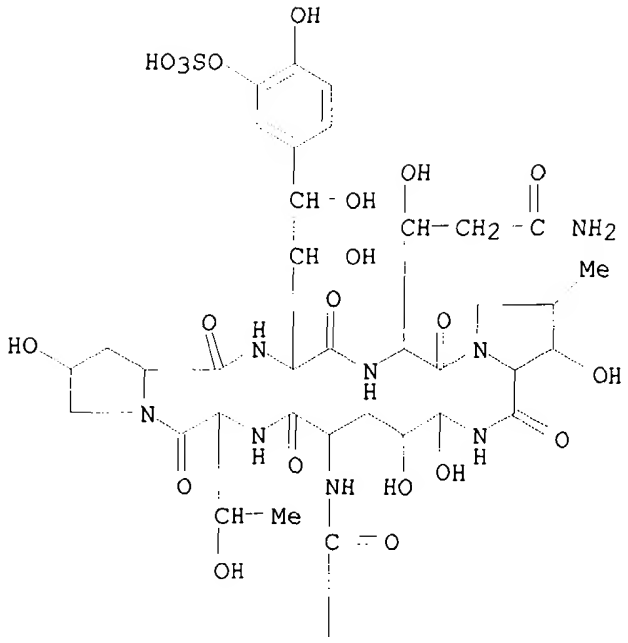

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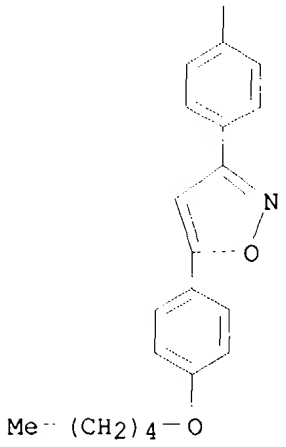

IT **235114-32-6D**, metabolites
RL: BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study)
(drug interactions of micafungin in vitro)

RN 235114-32-6 HCAPLUS

CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]- (9CI) (CA

INDEX NAME)

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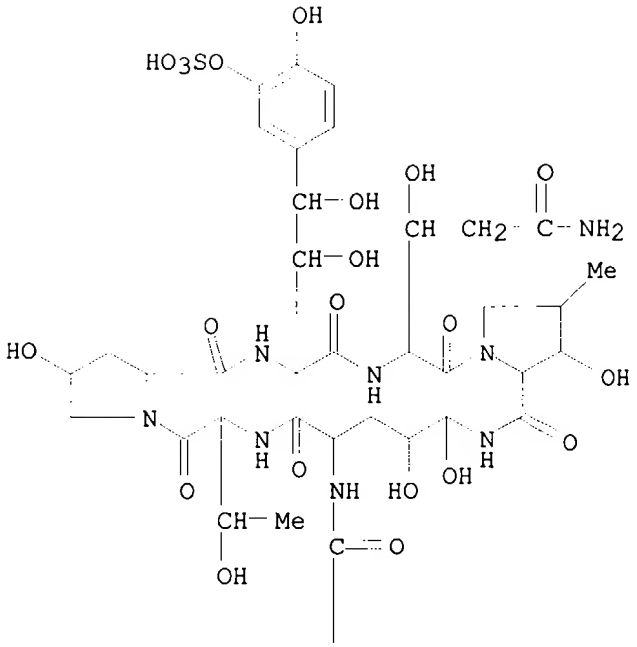
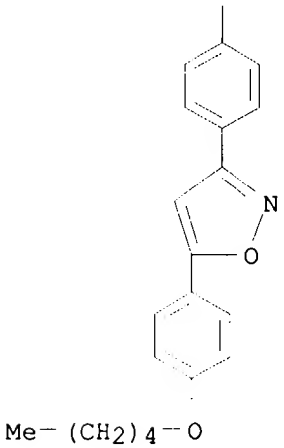


PAGE 2-A



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L13 ANSWER 6 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:6319 HCAPLUS
DOCUMENT NUMBER: 139:143383
TITLE: Combination effect of micafungin with **amphotericin B,**

itraconazole, and **fluconazole**

AUTHOR(S): Niki, Yoshihito; Yoshida, Koichiro; Matsushima, Toshiharu; Nakajima, Masamitsu; Nakai, Toru; Otomo, Kazumi; Wakai, Yoshimi; Matsumoto, Satoru; Hatano, Kazuo; Ikeda, Fumiaki; Mutoh, Seitaro

CORPORATE SOURCE: Division of Respiratory Diseases, Department of Medicine, Kawasaki Medical School, Japan

SOURCE: Nippon Kagaku Ryoho Gakkai Zasshi (2002), 50(Suppl. 1), 58-67
CODEN: NKRZE5; ISSN: 1340-7007

PUBLISHER: Nippon Kagaku Ryoho Gakkai

DOCUMENT TYPE: Journal

LANGUAGE: Japanese

AB In vitro interactions between micafungin (MCFG) and **amphotericin B** (AMPH-B), **itraconazole** (ITCZ), and **fluconazole** (FLCZ) were evaluated using a checkerboard method based on the standard broth microdilution method M27-A recommended by the NCCLS. When MCFG was combined with AMPH-B, ITCZ, and FLCZ, additive interaction was observed for 41%, 85%, and 85% of Candida albicans isolates, resp., and either synergistic or additive interaction was observed for 67%, 87% and 13% of Aspergillus fumigatus isolates, resp. An excellent interaction was observed for Cryptococcus neoformans when MCFG was combined with AMPH-B, which was synergistic for 67% and additive for 33% of isolates tested. Antagonism was observed only in the MCFG-ITCZ combination for 83% of C. neoformans. For the purpose of in vivo validation of the in vitro interaction of MCFG and AMPH-B, we evaluated the efficacy of combination therapy of the 2 drugs against a mouse model of pulmonary aspergillosis induced by A. fumigatus IFM 40836, against which the combination yielded an additive interaction in vitro. Combination therapy with MCFG (2 mg/kg) and AMPH-B (0.5 mg/kg) produced a significant decrease in fungal colony count in the lung compared to not only the control group but also to either dose alone 6 days after infection. The combination also strongly suppressed histopathol. determined pulmonary lesion, hyphal elongation and neutrophil infiltration. Furthermore, combination therapy of MCFG (1 mg/kg) and AMPH-B (0.25 mg/kg) was more effective than both MCFG alone (2 mg/kg) and AMPH-B alone (0.5 mg/kg), which were both double the dose used in the combination treatment. These results suggest that the interaction of MCFG and AMPH-B in this pulmonary aspergillosis model was synergistic. In conclusion, MCFG showed an excellent interaction with AMPH-B both in vitro and in vivo, suggesting that combination therapy with these 2 drugs might have utility for the treatment of severe deep-seated fungal infections. In addition, MCFG may have clin. usefulness in combination therapy with other com. available antifungal agents.

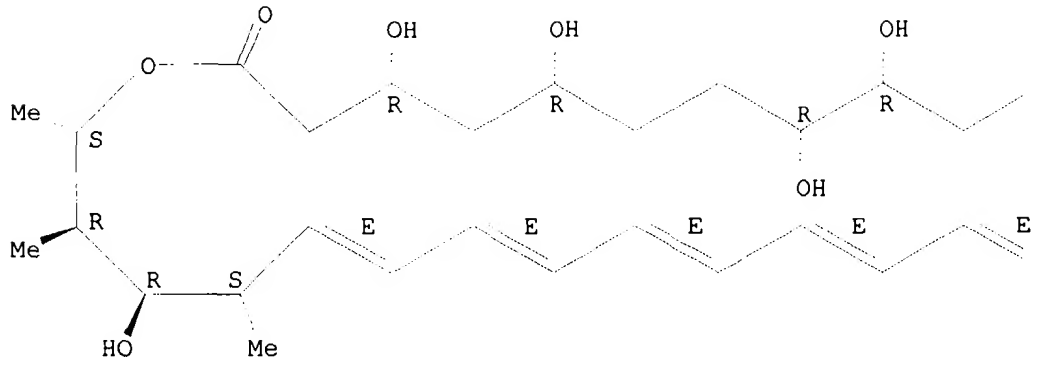
IT **1397-89-3, Amphotericin B**
84625-61-6, Itraconazole 86386-73-4,
Fluconazole 235114-32-6, Micafungin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(combination antifungal effect of micafungin with **amphotericin B, itraconazole**, and **fluconazole**)

RN 1397-89-3 HCAPLUS

CN Amphotericin B (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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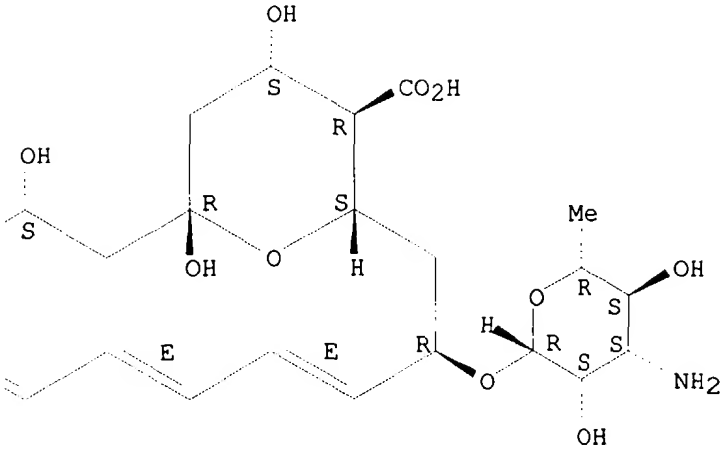

RN 84625-61-6 HCAPLUS
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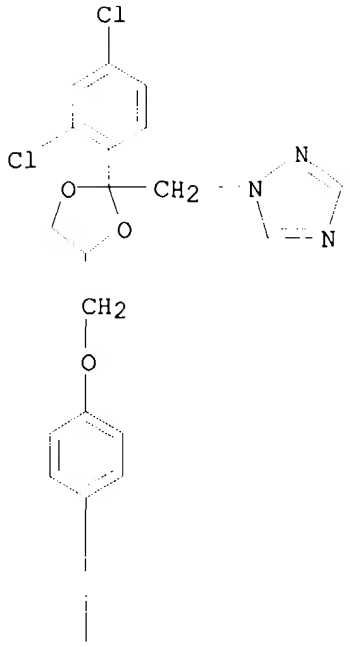
PAGE 1-A



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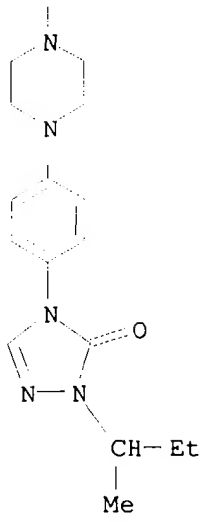
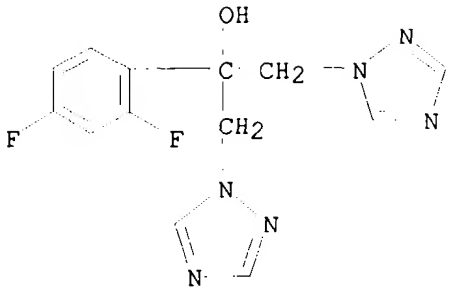
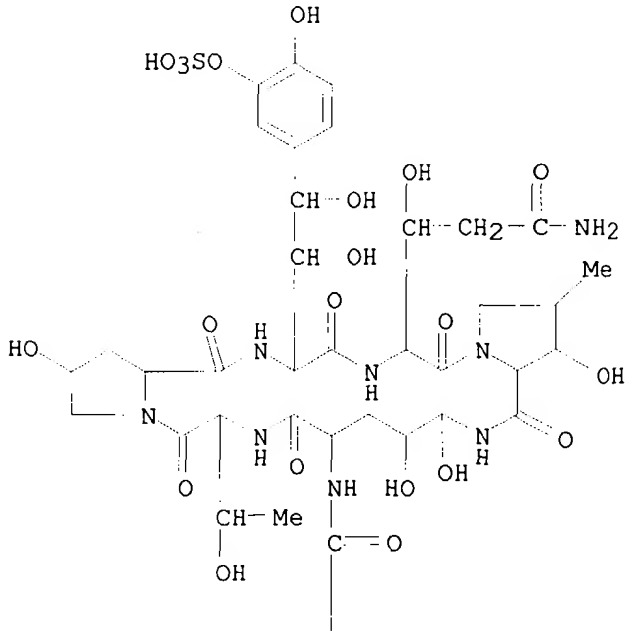


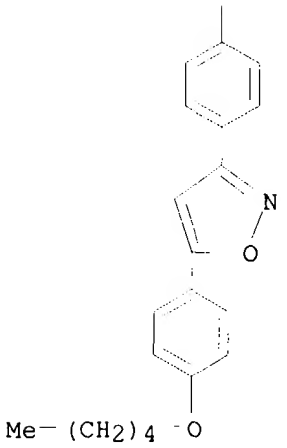
RN 86386-73-4 HCAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)- (9CI) (CA INDEX NAME)



RN 235114-32-6 HCAPLUS
CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]- (9CI) (CA INDEX NAME)

PAGE 1-A





L13 ANSWER 7 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:6317 HCAPLUS
DOCUMENT NUMBER: 138:82935
TITLE: Therapeutic effect of micafungin on oropharyngeal candidiasis in congenitally immunodeficient mice
AUTHOR(S): Nakai, Toru; Hatano, Kazuo; Ikeda, Fumiaki; Mutoh, Seitaro
CORPORATE SOURCE: Medicinal Biology Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., Osaka, 532-8514, Japan
SOURCE: Nippon Kagaku Ryoho Gakkai Zasshi (2002), 50(Suppl. 1), 48-53
CODEN: NKRZE5; ISSN: 1340-7007
PUBLISHER: Nippon Kagaku Ryoho Gakkai
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB The therapeutic efficacy of micafungin against a murine model of oropharyngeal candidiasis was evaluated. Oropharyngeal candidiasis was induced in congenitally immunodeficient N:NIH-bg-nu-xid BR mice by oral inoculation of Candida albicans cells for 4 days. The mice were i.v. administered micafungin, **fluconazole**, or saline alone from 13 to 23 days after initial inoculation, twice daily. Therapeutic effect was evaluated as reduction in tissue colony count and histopathol. in the tongue 1 day and 8 days after the end of treatment. From the initial treatment to 8 days after the end of treatment, saline-treated control mice displayed 104 to 105 C. albicans in the tongue. Histopathol. examination revealed continuous infection of C. albicans pseudohyphae in keratinized mucosal layers of the tongue throughout the expts. In addition, this infection was accompanied by infiltration of inflammatory cells after the end of treatment. In this mouse model, micafungin showed therapeutic efficacy at 2 mg/kg or higher 1 day after the end of treatment, as demonstrated by a significant reduction in viable colony count and repaired normal morphol. of the tongue. After an 8 day non-treatment interval, 5 mg/kg or higher doses were still effective in terms of both colony count and histopathol., although increased

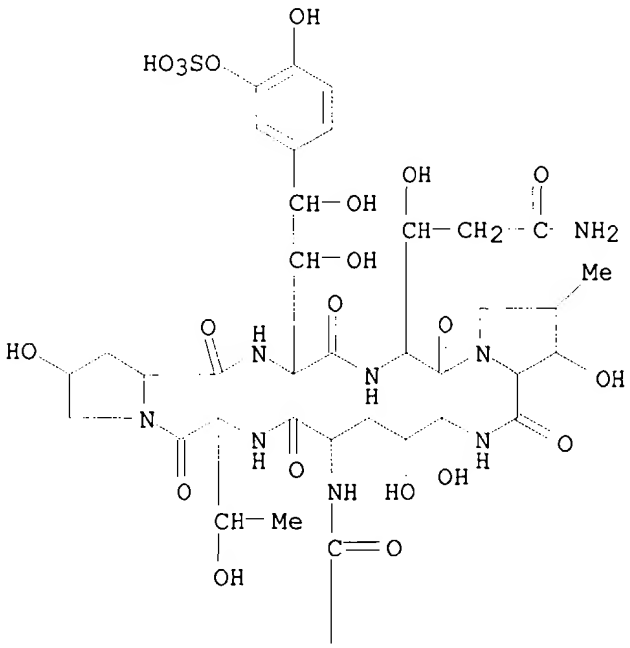
counts and re-infected tongue mucosa were observed in mice treated with 2 mg/kg micafungin. The efficacy of micafungin at 5 mg/kg or higher was comparable to that of **fluconazole** at 20 mg/kg. These results suggest that micafungin shows and eradicative effect at a lower dose than **fluconazole** in this mouse model, therefore it has potential usefulness a a therapeutic drug with a low incidence of relapse.

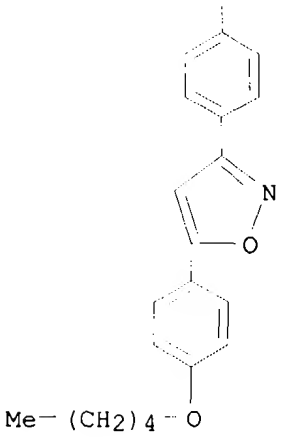
IT **235114-32-6**, Micafungin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(therapeutic effect of micafungin on oropharyngeal candidiasis in congenitally immunodeficient mice)

RN 235114-32-6 HCAPLUS

CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]- (9CI) (CA INDEX NAME)

PAGE 1-A





L13 ANSWER 8 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:6315 HCAPLUS
DOCUMENT NUMBER: 138:82934
TITLE: Efficacy of micafungin, a new lipopeptide antifungal agent, in mouse models of pulmonary aspergillosis
AUTHOR(S): Matsumoto, Satoru; Wakai, Yoshimi; Watabe, Etsuko; Maki, Katsuyuki; Ikeda, Fumiaki; Tawara, Shuichi; Mutoh, Seitaro; Matsumoto, Fumio; Kuwahara, Shogo
CORPORATE SOURCE: Medicinal Biology Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., Osaka, 532-8514, Japan
SOURCE: Nippon Kagaku Ryoho Gakkai Zasshi (2002), 50(Suppl. 1), 37-42
CODEN: NKRZE5; ISSN: 1340-7007
PUBLISHER: Nippon Kagaku Ryoho Gakkai
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB The efficacy of micafungin (MCFG), a novel water-soluble lipopeptide, was evaluated in mouse models of pulmonary aspergillosis, and compared with that of **amphotericin B** (AMPH-B), **fluconazole** (FLCZ), and **itraconazole** (ITCZ). In pulmonary aspergillosis in mice immunosuppressed by cyclophosphamide, MCFG significantly prolonged the survival of mice infected intranasally with Aspergillus fumigatus at doses of 0.5 and 1 mg/kg ($P < 0.0125$). In mice with pulmonary aspergillosis caused by A. fumigatus, MCFG exhibited 50% EDs (ED50s) in the range of 0.26 to 0.45 mg/kg 15 days after infection, which is comparable to the efficacy of AMPH-B (ED50s; 0.25 to 0.46 mg/kg), and superior to FLCZ and ITCZ. The ED50 of MCFG was comparable to that of AMPH-B in mice immunosuppressed by 5-fluorouracil, however, it was 4.1 times inferior to that of AMPH-B in mice immunosuppressed by hydrocortisone. When treatment with MCFG was initiated 1 day after infection, the ED50 of MCFG was 1.21 mg/kg, which was 2.4 times inferior to that of AMPH-B and 3.8 times inferior to that of MCFG if initiated 1.5 h after infection. These results indicate that MCFG

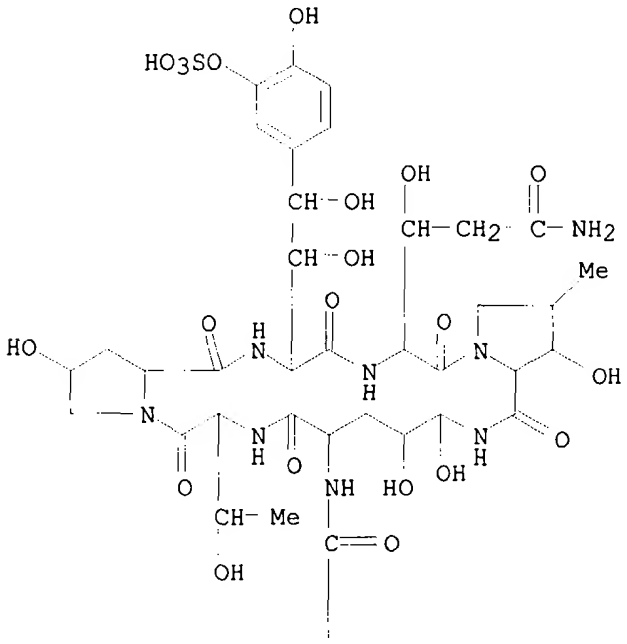
may be a potent parenteral administered antifungal agent for pulmonary aspergillosis, with efficacy comparable or slightly inferior to that of AMPH-B, but superior to that of FLCZ and ITCZ.

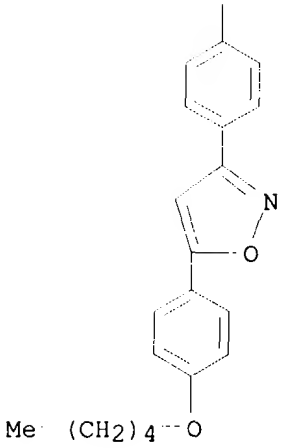
IT **235114-32-6**, Micafungin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(efficacy of micafungin in mouse models of pulmonary aspergillosis)

RN 235114-32-6 HCAPLUS

CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]- (9CI) (CA INDEX NAME)

PAGE 1-A





L13 ANSWER 9 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:6314 HCAPLUS
DOCUMENT NUMBER: 138:66183
TITLE: Efficacy of micafungin, a new lipopeptide antifungal agent, in mouse models of disseminated candidiasis and aspergillosis
AUTHOR(S): Matsumoto, Satoru; Wakai, Yoshimi; Watabe, Etsuko; Maki, Katsuyuki; Ikeda, Fumiaki; Tawara, Shuichi; Mutoh, Seitaro; Matsumoto, Fumio; Kuwahara, Shogo
CORPORATE SOURCE: Medicinal Biology Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., Osaka, 532-8514, Japan
SOURCE: Nippon Kagaku Ryoho Gakkai Zasshi (2002), 50(Suppl. 1), 30-36
CODEN: NKRZE5; ISSN: 1340-7007
PUBLISHER: Nippon Kagaku Ryoho Gakkai
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB The efficacy of micafungin (MCFG), a novel water-soluble lipopeptide, was evaluated in mouse models of disseminated candidiasis and aspergillosis, and was compared with that of **amphotericin B** (AMPH-B), **fluconazole** (FLCZ), and **itraconazole** (ITCZ). In the candidiasis model in mice with granulocytopenia induced by cyclophosphamide, MCFG significantly prolonged the survival of mice infected i.v. with Candida albicans at doses of 0.125 mg/kg or higher ($P < 0.01$). In candidiasis and aspergillosis caused by C. albicans, C. glabrata, C. tropicalis, C. krusei, C. guilliermondii, and Aspergillus fumigatus, MCFG exhibited ED50s in the range of 0.14-1.61 mg/kg. These data were comparable or inferior to those of AMPH-B, but superior to FLCZ and ITCZ. In disseminated candidiasis in mice immunosuppressed by cyclophosphamide, hydrocortisone or 5-fluorouracil, the ED50s of MCFG were 0.14-0.33 mg/kg, superior to ITCZ and FLCZ, but inferior to AMPH-B. In a target organ kidney assay, a single injection of MCFG at a doses of 0.5 or 1.0 mg/kg significantly reduced the yeast viable cell counts in the kidney 24 h after treatment compared to

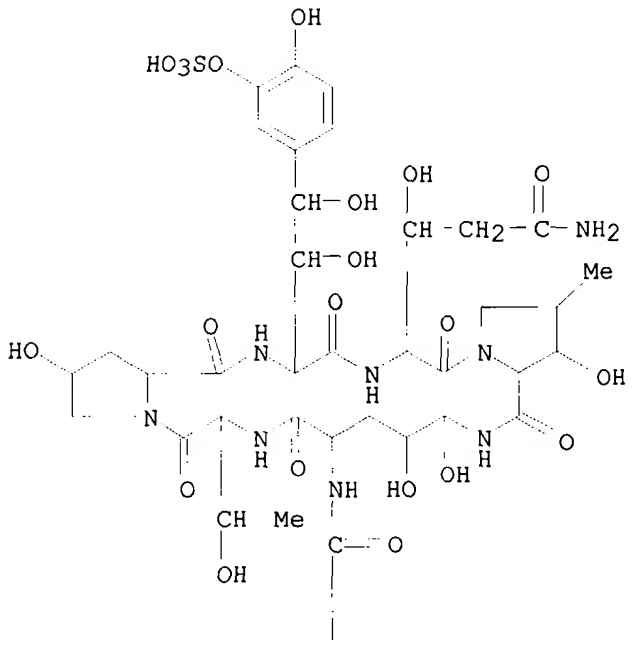
the yeast counts before treatment, with an efficacy comparable to AMPH-B. These results indicate that MCFG is a potent parenteral administered therapeutic agent for disseminated candidiasis and aspergillosis in immunosuppressed mice. The efficacy of MCFG was superior to that of FLCZ and ITCZ, but comparable or slightly inferior to that of AMPH-B.

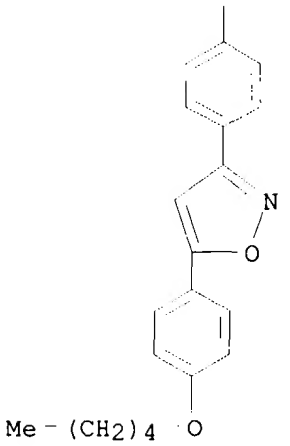
IT **235114-32-6**, Micafungin
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(efficacy of micafungin in mouse models of disseminated candidiasis and aspergillosis)

RN 235114-32-6 HCAPLUS

CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]- (9CI) (CA INDEX NAME)

PAGE 1-A





L13 ANSWER 10 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:6312 HCAPLUS
DOCUMENT NUMBER: 138:86338
TITLE: In vitro activity of a new lipopeptide antifungal agent, micafungin against a variety of clinically important fungi
AUTHOR(S): Ikeda, Fumiaki; Otomo, Kazumi; Nakai, Tohru; Morishita, Yoshihiko; Maki, Katsuyuki; Tawara, Shuichi; Mutoh, Seitaro; Matsumoto, Fumio; Kuwahara, Shogo
CORPORATE SOURCE: Medical Biology Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., Osaka, 532-8514, Japan
SOURCE: Nippon Kagaku Ryoho Gakkai Zasshi (2002), 50(Suppl. 1), 8-19
CODEN: NKRZE5; ISSN: 1340-7007
PUBLISHER: Nippon Kagaku Ryoho Gakkai
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB The in vitro antifungal activity and spectrum of micafungin (MCFG) were compared with those of **amphotericin-B** (AMPH-B), **fluconazole** (FLCZ), and **itraconazole** (ITCZ) using a broth microdilution method as specified by the National Committee for Clin. Laboratory Stds. (NCCLS) document M 27-A. MCFG exhibited broad-spectrum activity against clin. important pathogens including Candida species and Aspergillus species, and its MIC90 levels against C. albicans (including FLCZ-resistant C. albicans), C. tropicalis, C. glabrata, C. krusei, and Aspergillus species were ≤0.125 μg/mL, which were lower than those for the other antifungal agents tested. The MIC90 levels of MCFG against C. parapsilosis and C. guilliermondii were 4 and 2 μg/mL, resp., which were comparable to or higher than those for the other antifungal agents tested. MCFG exhibited concentration-independent fungicidal activity at concns. higher than the MIC against most Candida species. In contrast, the MICs of MCFG against A. fumigatus isolates were much higher than the MICs of the other agents, indicating that its action is fungistatic against this species. MCFG showed moderate to weak activity against most Dematiaceous

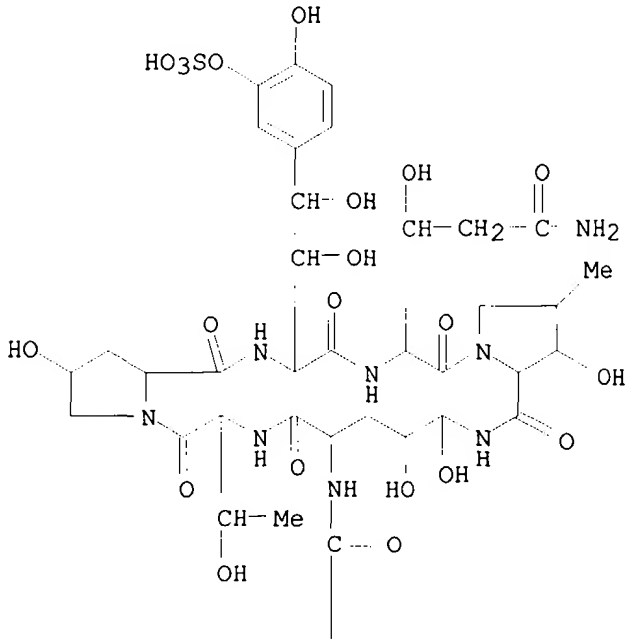
fungi and had no activity against Cryptococcus neoformans, Trichosporon species, Fusarium solani, Pseudallesheria boydii, and Zygomycetes. Although MCFG showed potent activity against the mycelial form of dimorphic fungi, it had weak or no activity against their yeast-like form. Neither the pH of the test medium nor the inoculum size greatly affected the MIC values of MCFG, while addition of human serum or human serum albumin increased the MIC values against Candida species and A. fumigatus. In expts. on resistance induction, the MIC of MCFG for C. albicans was not significantly changes; indicating that there is a low probability of MCFG-induced resistance.

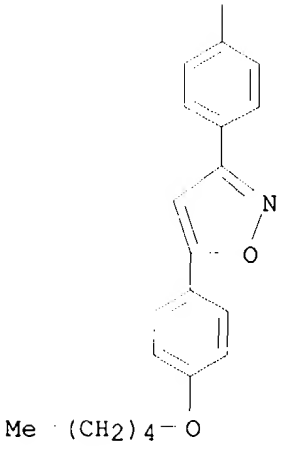
IT **235114-32-6**, Micafungin
RL: BSU (Biological study, unclassified); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vitro activity of new lipopeptide antifungal agent, micafungin against variety of clin. important fungi)

RN 235114-32-6 HCAPLUS

CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]- (9CI) (CA INDEX NAME)

PAGE 1-A





L13 ANSWER 11 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:937147 HCAPLUS
DOCUMENT NUMBER: 139:17145
TITLE: In vivo activity of micafungin in a persistently neutropenic murine model of disseminated infection caused by Candida tropicalis
AUTHOR(S): Warn, Peter A.; Sharp, Andrew; Morrissey, Graham; Denning, David W.
CORPORATE SOURCE: School of Medicine, University of Manchester, Manchester, M23 9PL, UK
SOURCE: Journal of Antimicrobial Chemotherapy (2002), 50(6), 1071-1074
CODEN: JACHDX; ISSN: 0305-7453
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Micafungin is a new echinocandin with broad-spectrum in vitro and in vivo antifungal activity against both Aspergillus and Candida species. We compared the activity of micafungin with that of **amphotericin B** and **fluconazole** in a persistently immunocompromised murine model of disseminated candidiasis against a strain of Candida tropicalis that was resistant to **amphotericin B** and **fluconazole** in vitro. Mice were rendered persistently neutropenic with multiple doses of cyclophosphamide and infected i.v. with C. tropicalis. Mice were treated with either i.p. **amphotericin B** (0.5-5 mg/kg per dose), oral **fluconazole** (50 mg/kg twice a day), i.v. micafungin (1-10 mg/kg per dose) or solvent control for 7 days. Mice were killed at 11 days post-infection and kidneys, lungs, brain and liver removed for quant. culture. Overall mortality in the model was low, with rates varying between 10% and 25% in treatment groups. Micafungin at doses between 2 and 10 mg/kg were the only regimes able to reduce cfu below the level of detection of tissues infected with C. tropicalis. Micafungin was well tolerated by the mice and was much more effective than **amphotericin B** or **fluconazole** against an **amphotericin B**-

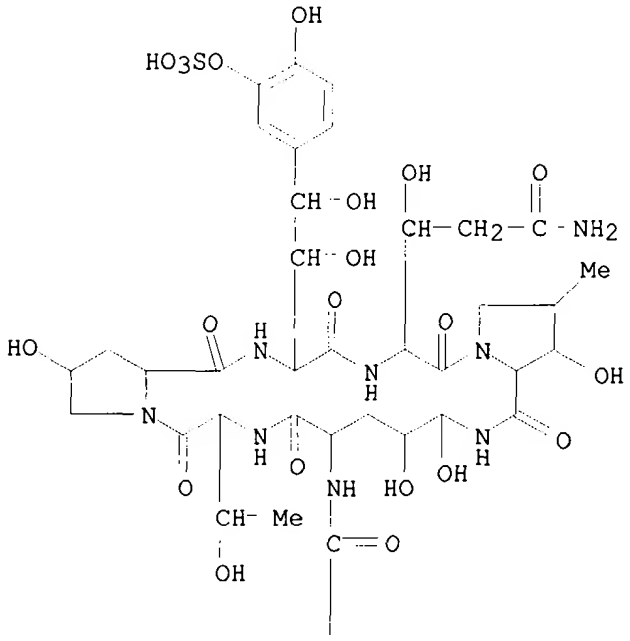
and **fluconazole**-resistant C. tropicalis.

IT **235114-32-6**, Micafungin
RL: ADV (Adverse effect, including toxicity); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(activity of micafungin in persistently neutropenic murine model of disseminated infection caused by Candida tropicalis)

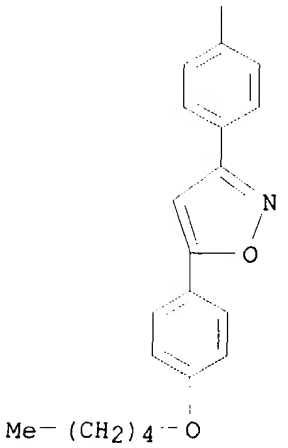
RN 235114-32-6 HCAPLUS

CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]- (9CI) (CA INDEX NAME)

PAGE 1-A



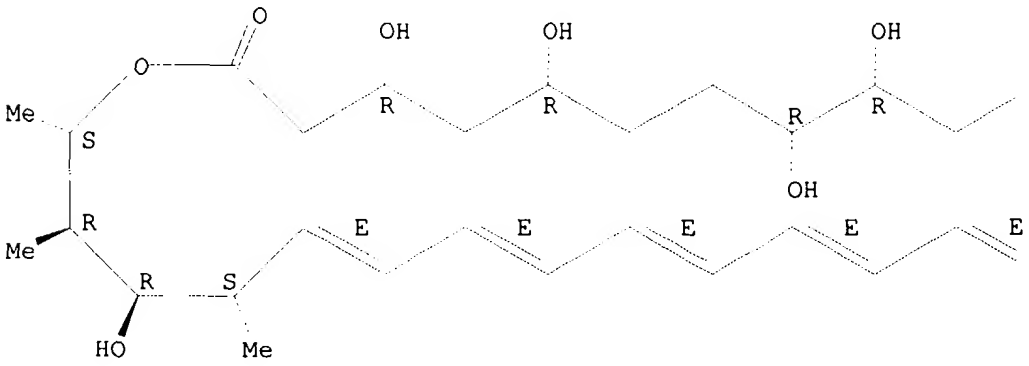
PAGE 2-A

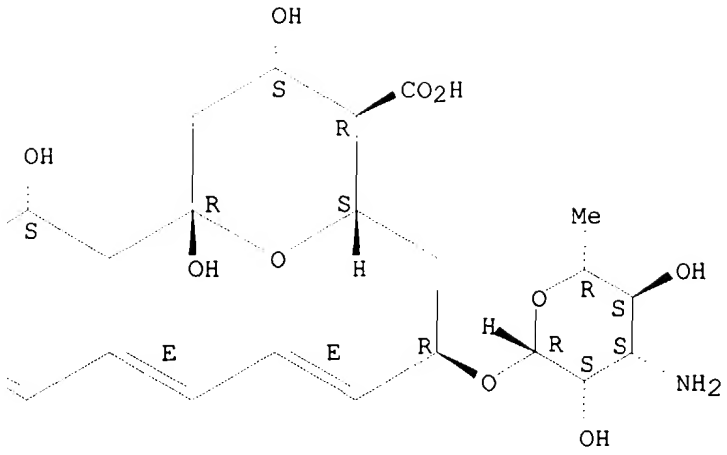


IT **1397-89-3, Amphotericin B**
86386-73-4, Fluconazole
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(activity of micafungin in persistently neutropenic murine model of disseminated infection caused by Candida tropicalis)
RN 1397-89-3 HCAPLUS
CN Amphotericin B (8CI, 9CI) (CA INDEX NAME)

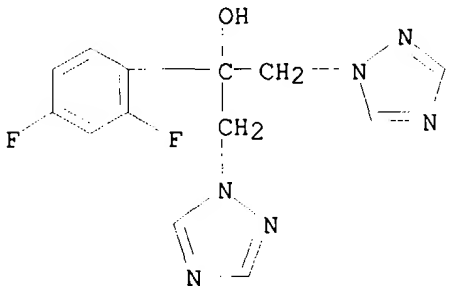
Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A





RN 86386-73-4 HCAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 12 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:557413 HCAPLUS
DOCUMENT NUMBER: 138:198158
TITLE: Effect of Micafungin (FK463) on Candida albicans Adherence to Epithelial Cells
AUTHOR(S): Borg-von Zepelin, Margarete; Zaschke, Karen; Gross, Uwe; Monod, Michel; Mueller, Frank-Michael C.
CORPORATE SOURCE: Department of Bacteriology, Goettingen, Germany
SOURCE: Chemotherapy (Basel, Switzerland) (2002), 48(3), 148-153
CODEN: CHTHBK; ISSN: 0009-3157
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background: Adherence is considered a major virulence trait of

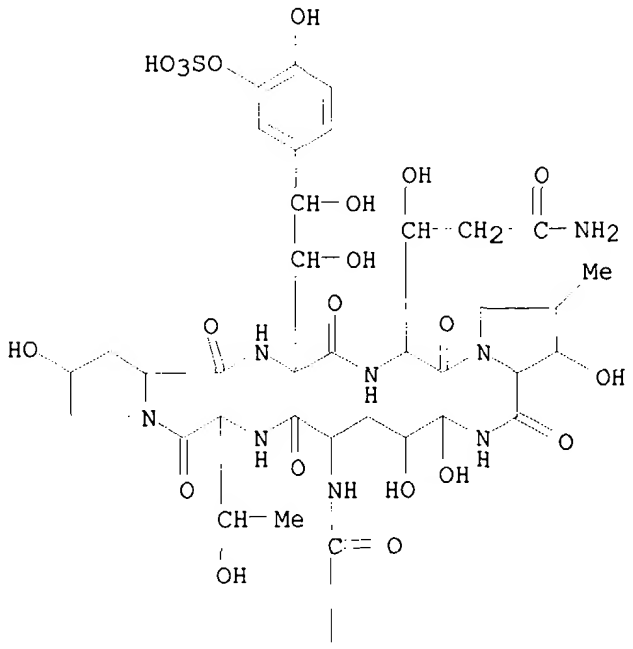
Candida albicans. FK463 is a new investigational i.v. antifungal of the '*candin family*' with potent in vitro and in vivo activity against Candida spp. Objective: The aim of the present study was to investigate the effect of Micafungin (FK463) on Candida adherence to epithelial cells of azole-sensitive and azole-resistant C. albicans isolates. Methods: An in vitro assay using microtest plate technol. and fluorescence measurement was developed to compare the adherence of C. albicans SC5314 and of paired C. albicans isolates to epithelial cells in the presence and in the absence of FK463. Results: FK463 showed a marked inhibitory effect on the adherence of C. albicans SC5314. The addition of FK463 reduced the adherence of C. albicans SC5314 to 90% of the value of control without drug. A dose-dependent adherence inhibition was observed with FK463 in the range of 10-0.015 μg ml-1. The comparison of paired C. albicans isolates, either a **fluconazole**-susceptible and a **fluconazole**-resistant isolate of one patient, revealed no significant difference in the adherence behavior between azole-susceptible and azole-resistant. Conclusion: Micafungin (FK463) has the capacity to reduce adherence of C. albicans azole-susceptible and azole-resistant strains to epithelial cells.

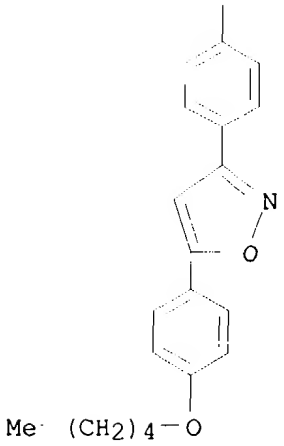
IT **208538-73-2**, FK463
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(effect of Micafungin (FK463) on Candida albicans adherence to epithelial cells)

RN 208538-73-2 HCAPLUS

CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]-, monosodium salt (9CI) (CA INDEX NAME)

PAGE 1-A





REFERENCE COUNT: 21 THERE ARE 21 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 13 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:556104 HCAPLUS
DOCUMENT NUMBER: 137:109489
TITLE: Compositions comprising a polypeptide and an active agent
INVENTOR(S): Piccariello, Thomas; Olon, Lawrence P.; Kirk, Randal J.
PATENT ASSIGNEE(S): USA
SOURCE: U.S. Pat. Appl. Publ., 34 pp.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2002099013	A1	20020725	US 2001-933708	20010822

PRIORITY APPLN. INFO.:

US 2000-247556P	P	20001114
US 2000-247558P	P	20001114
US 2000-247559P	P	20001114
US 2000-247560P	P	20001114
US 2000-247561P	P	20001114
US 2000-247594P	P	20001114
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US	2000-247928P	P	20001114
US	2000-247929P	P	20001114
US	2000-247930P	P	20001114

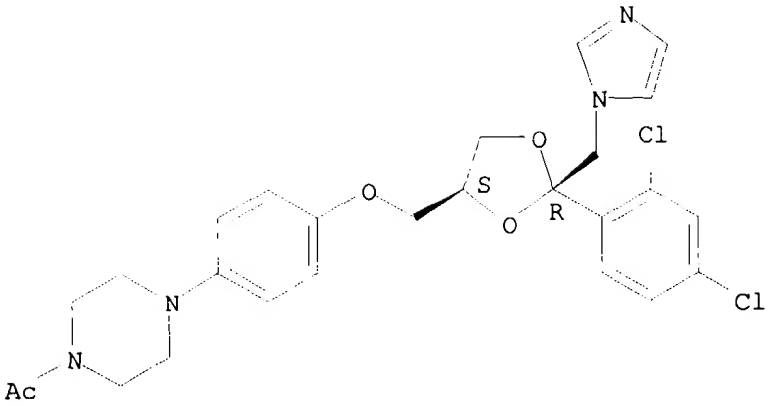
AB Claimed are compns. comprising a polypeptide and an active agent covalently attached to the polypeptide and a method for delivery of an active agent to a patient by administering the composition to the patient. The peptide is a homopolymer of a naturally occurring amino acid or a heteropolymer of two or more naturally occurring amino acids. In an example, (Glu)n-cephalexin was prepared from Glu(OBut)NCA and cephalexin hydrochloride.

IT **65277-42-1, Ketoconazole 84625-61-6, Itraconazole 86386-73-4, Fluconazole 137234-62-9, Voriconazole 171228-49-2,** Posaconazole **208538-73-2,** FK 463
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising a polypeptide and an active agent)

RN 65277-42-1 HCAPLUS

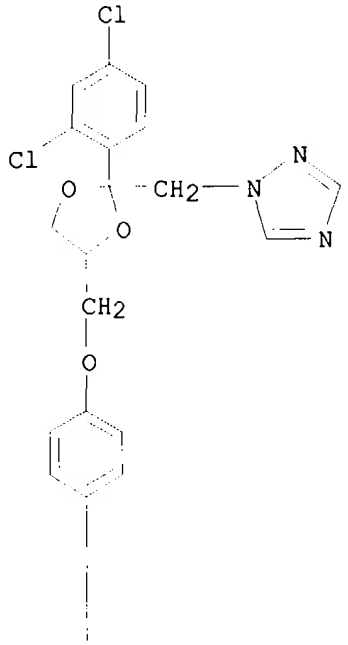
CN Piperazine, 1-acetyl-4-[4-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-, rel- (9CI) (CA INDEX NAME)

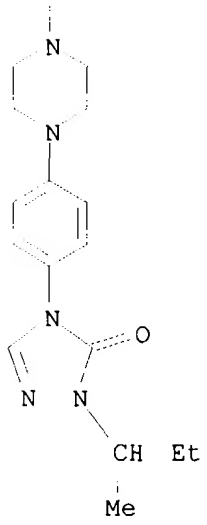
Relative stereochemistry.



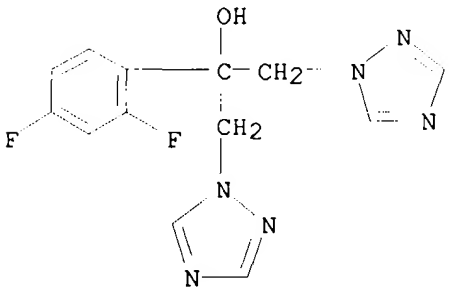
RN 84625-61-6 HCAPLUS
CN 3H-1,2,4-Triazol-3-one, 4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)- (9CI) (CA INDEX NAME)

PAGE 1-A



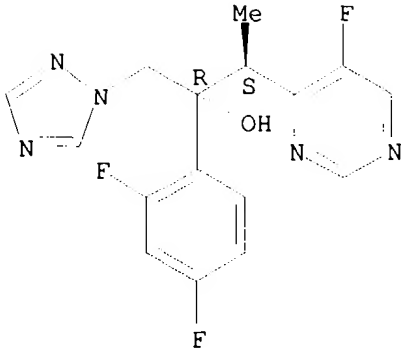


RN 86386-73-4 HCAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)- (9CI) (CA INDEX NAME)



RN 137234-62-9 HCAPLUS
CN 4-Pyrimidineethanol, α-(2,4-difluorophenyl)-5-fluoro-β-methyl-α-(1H-1,2,4-triazol-1-ylmethyl)-, (αR,βS)-(9CI) (CA INDEX NAME)

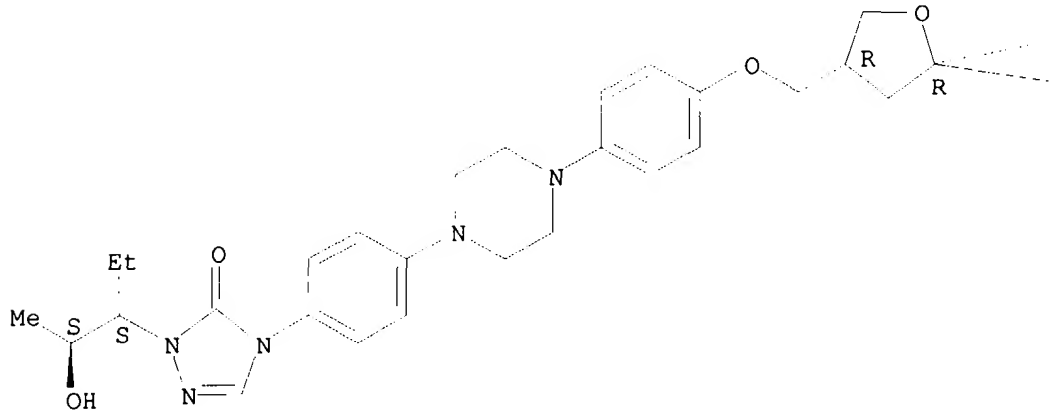
Absolute stereochemistry.



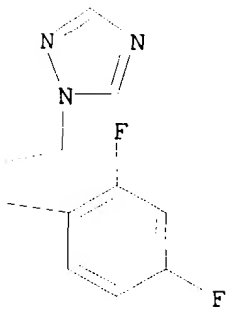
RN 171228-49-2 HCAPLUS
CN D-threo-Pentitol, 2,5-anhydro-1,3,4-trideoxy-2-C-(2,4-difluorophenyl)-4-[[4-[4-[4-[1-[(1S,2S)-1-ethyl-2-hydroxypropyl]-1,5-dihydro-5-oxo-4H-1,2,4-triazol-4-yl]phenyl]-1-piperazinyl]phenoxy]methyl]-1-(1H-1,2,4-triazol-1-yl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A

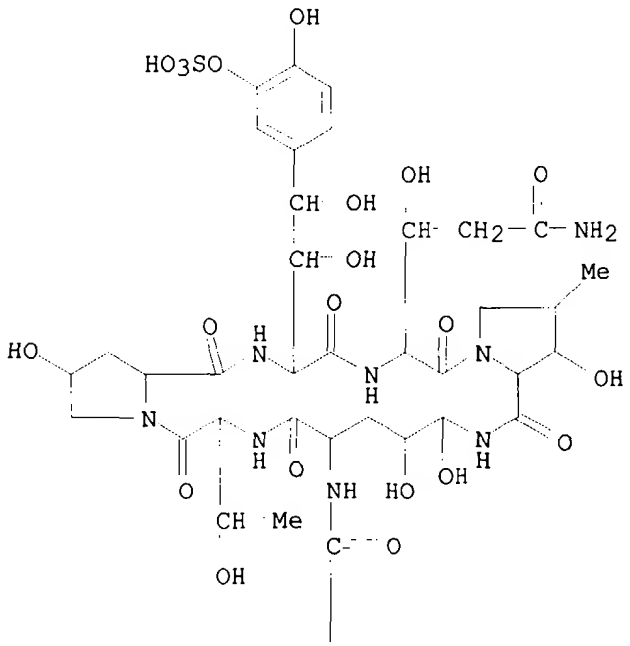


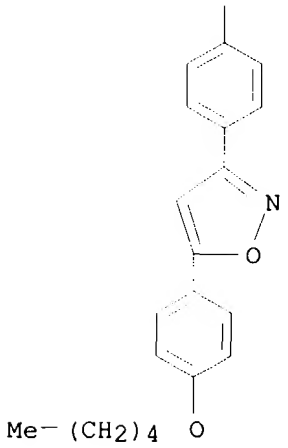
PAGE 1-B



RN 208538-73-2 HCAPLUS
CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]-, monosodium salt (9CI) (CA INDEX NAME)

PAGE 1-A





L13 ANSWER 14 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:555111 HCAPLUS
DOCUMENT NUMBER: 137:213466
TITLE: In vitro activity of three new triazoles and one echinocandin against Candida bloodstream isolates from cancer patients
AUTHOR(S): Laverdiere, M.; Hoban, D.; Restieri, C.; Habel, F.
CORPORATE SOURCE: Department of Microbiology-Infectious Diseases, Hopital Maisonneuve-Rosemont, Montreal, QC, H1T 2M4, Can.
SOURCE: Journal of Antimicrobial Chemotherapy (2002), 50(1), 119-123
CODEN: JACHDX; ISSN: 0305-7453
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The in vitro activities of **voriconazole**, posaconazole, ravuconazole, and micafungin were compared with those of **fluconazole**, **itraconazole**, **ketoconazole**, **flucytosine**, and **amphotericin B** against 164 candidemia isolates recovered from cancer patients in 2 Canadian centers. The MIC50 results for ravuconazole, **voriconazole**, posaconazole and micafungin were 0.01, 0.03, 0.12 and 0.25 mg/L, resp. The new antifungal agents showed substantial activity against isolates demonstrating in vitro resistance to **fluconazole** and **itraconazole**. These results suggest that the newer antifungal agents possess promising activity against invasive Candida isolates, particularly against those with reduced susceptibility to **fluconazole** and **itraconazole**.

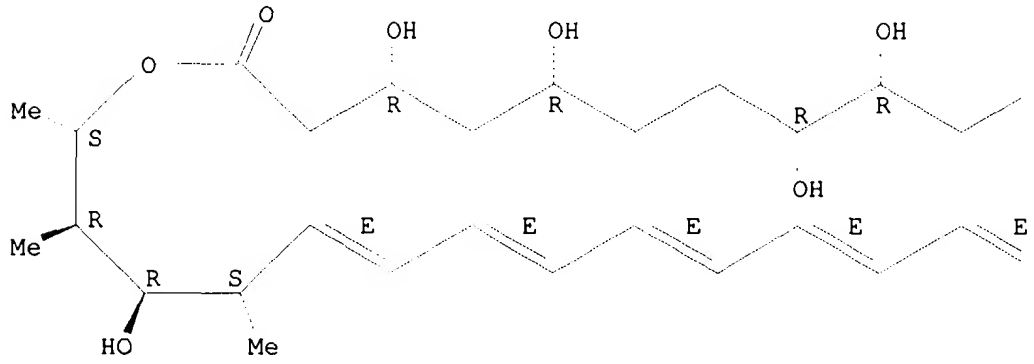
IT **1397-89-3, Amphotericin B**
2022-85-7, Flucytosine 65277-42-1,
Ketoconazole 84625-61-6, Itraconazole

86386-73-4, Fluconazole 137234-62-9,
Voriconazole 171228-49-2, Posaconazole
182760-06-1, Ravuconazole **235114-32-6,** Micafungin
RL: BSU (Biological study, unclassified); THU (Therapeutic use);
BIOL (Biological study); USES (Uses)
(antifungal activity of triazoles and micafungin compared with common fungicides against Candida)

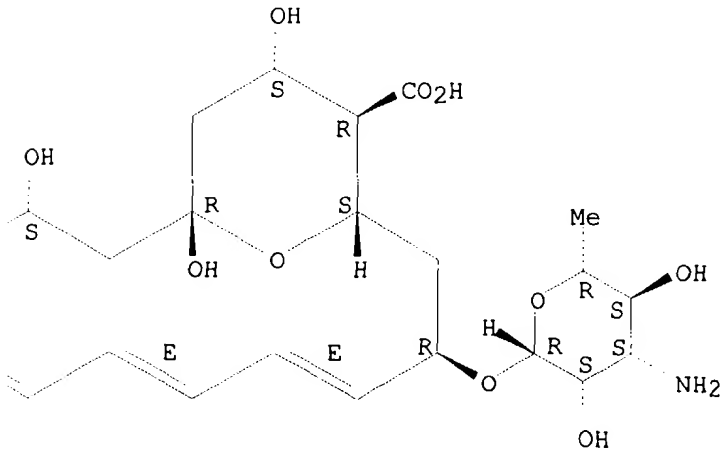
RN 1397-89-3 HCAPLUS
CN Amphotericin B (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A

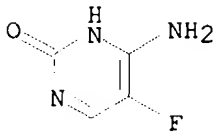


PAGE 1-B



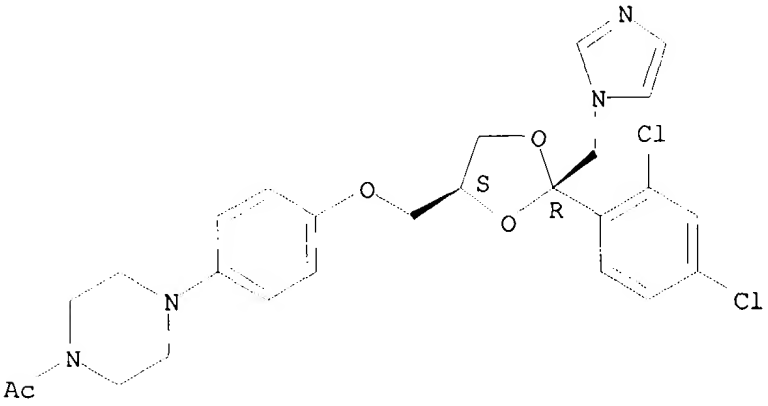
RN 2022-85-7 HCAPLUS

CN 2(1H)-Pyrimidinone, 4-amino-5-fluoro- (9CI) (CA INDEX NAME)



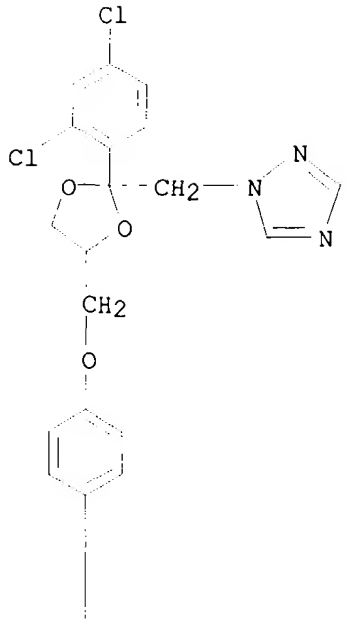
RN 65277-42-1 HCAPLUS
CN Piperazine, 1-acetyl-4-[4-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

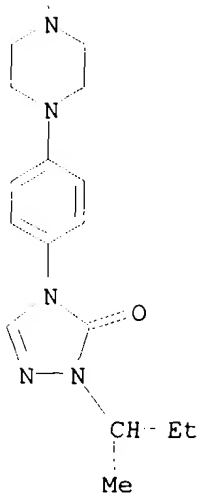


RN 84625-61-6 HCAPLUS
CN 3H-1,2,4-Triazol-3-one, 4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)- (9CI) (CA INDEX NAME)

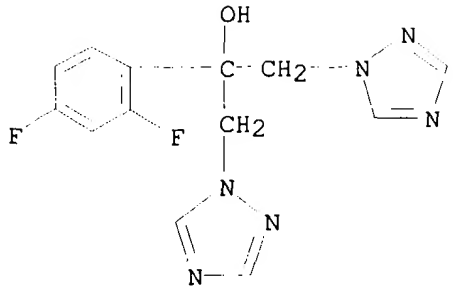
PAGE 1-A



PAGE 2-A

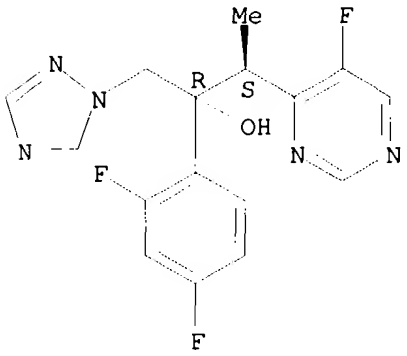


RN 86386-73-4 HCAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)- (9CI) (CA INDEX NAME)



RN 137234-62-9 HCAPLUS
CN 4-Pyrimidineethanol, α-(2,4-difluorophenyl)-5-fluoro-β-methyl-α-(1H-1,2,4-triazol-1-ylmethyl)-, (αR,βS)-(9CI) (CA INDEX NAME)

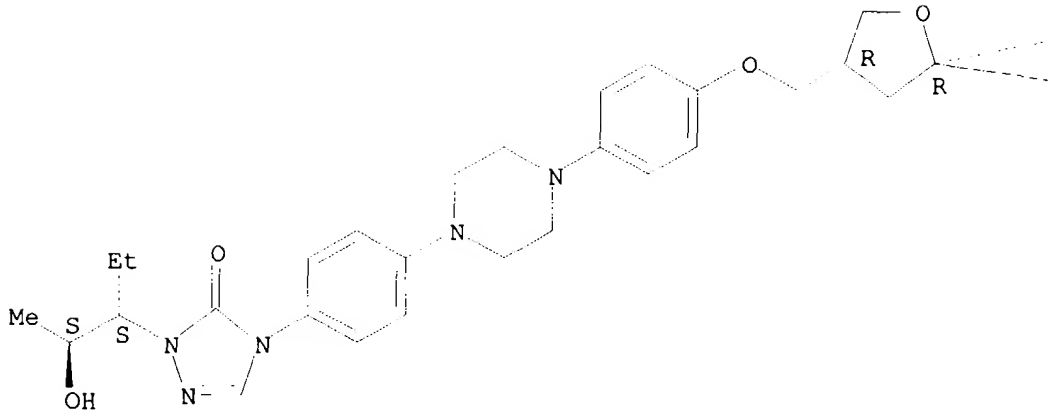
Absolute stereochemistry.



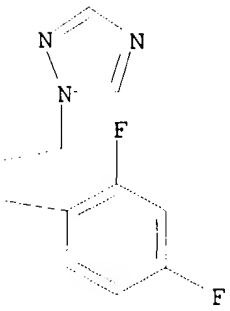
RN 171228-49-2 HCAPLUS
CN D-threo-Pentitol, 2,5-anhydro-1,3,4-trideoxy-2-C-(2,4-difluorophenyl)-4-[[4-[4-[4-[1-[(1S,2S)-1-ethyl-2-hydroxypropyl]-1,5-dihydro-5-oxo-4H-1,2,4-triazol-4-yl]phenyl]-1-piperazinyl]phenoxy]methyl]-1-(1H-1,2,4-triazol-1-yl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A

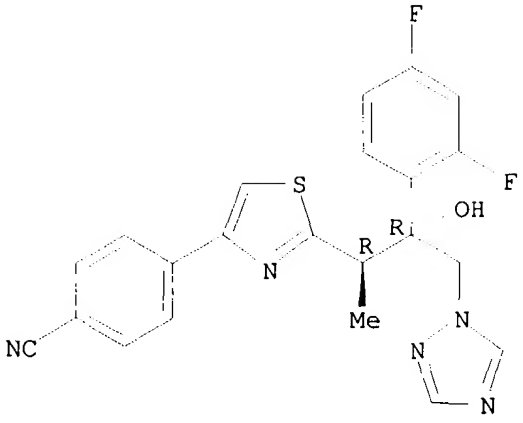


PAGE 1-B



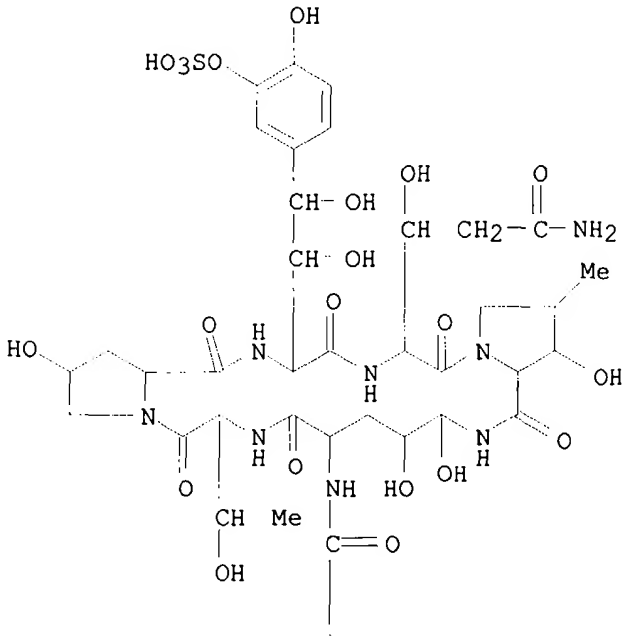
RN 182760-06-1 HCAPLUS
CN Benzonitrile, 4-[2-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-thiazolyl]- (9CI) (CA INDEX NAME)

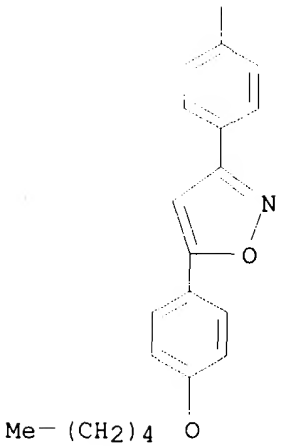
Absolute stereochemistry. Rotation (-).



RN 235114-32-6 HCAPLUS
CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]- (9CI) (CA INDEX NAME)

PAGE 1-A





REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 15 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:414526 HCAPLUS
DOCUMENT NUMBER: 137:319984
TITLE: Comparative antifungal activities and plasma pharmacokinetics of micafungin (FK463) against disseminated candidiasis and invasive pulmonary aspergillosis in persistently neutropenic rabbits
AUTHOR(S): Petraitis, Vidmantas; Petraitiene, Ruta; Groll, Andreas H.; Roussillon, Kristin; Hemmings, Melissa; Lyman, Caron A.; Sein, Tin; Bacher, John; Bekersky, Ihor; Walsh, Thomas J.
CORPORATE SOURCE: Immunocompromised Host Section, Pediatric Oncology Branch, National Cancer Institute, National Institutes of Health, Bethesda, MD, 20892, USA
SOURCE: Antimicrobial Agents and Chemotherapy (2002), 46(6), 1857-1869
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Micafungin (FK463) is an echinocandin that demonstrates potent in vitro antifungal activities against Candida and Aspergillus species. However, little is known about its comparative antifungal activities in persistently neutropenic hosts. We therefore investigated the plasma micafungin pharmacokinetics and antifungal activities of micafungin against exptl. disseminated candidiasis and invasive pulmonary aspergillosis in persistently neutropenic rabbits. The groups with disseminated candidiasis studied consisted of untreated controls (UCs); rabbits treated with desoxycholate **amphotericin B** (DAMB) at 1 mg/kg of body weight/day; or rabbits treated with micafungin at 0.25, 0.5, 1, and 2 mg/kg/day i.v. Compared with the UCs, rabbits treated with micafungin or DAMB

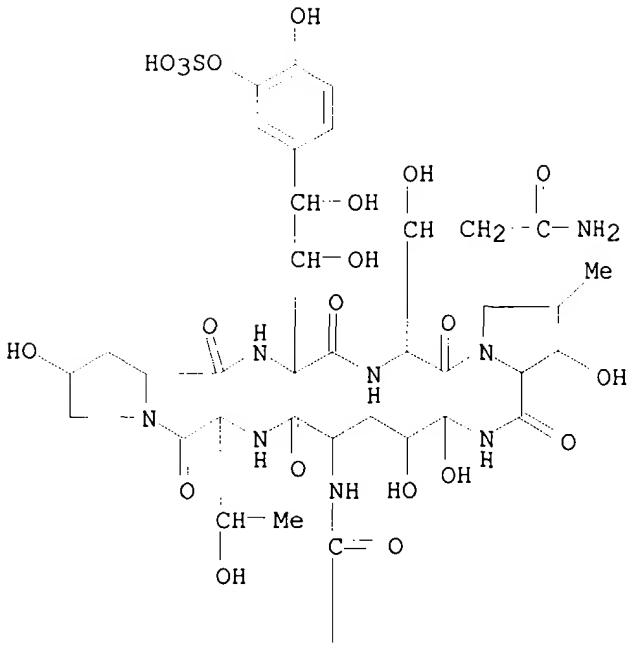
showed significant dosage-dependent clearance of Candida albicans from the liver, spleen, kidney, brain, eye, lung, and vena cava. These in vivo findings correlated with the results of in vitro time-kill assays that demonstrated that micafungin has concentration-dependent fungicidal activity. The groups with invasive pulmonary aspergillosis studied consisted of UCs; rabbits treated with DAMB; rabbits treated with **liposomal amphotericin B** (LAMB) at 5 mg/kg/day; and rabbits treated with micafungin at 0.5, 1, and 2 mg/kg/day. In comparison to the significant micafungin dosage-dependent reduction of the residual burden (in log CFU per g) of C. albicans in tissue, micafungin-treated rabbits with invasive pulmonary aspergillosis had no reduction in the concentration of Aspergillus fumigatus in tissue. DAMB and LAMB significantly reduced the burdens of C. albicans and A. fumigatus in tissues ($P < 0.01$). Persistent galactomannan antigenemia in micafungin-treated rabbits correlated with the presence of an elevated burden of A. fumigatus in pulmonary tissue. By comparison, DAMB- and LAMB-treated animals had significantly reduced circulating galactomannan antigen levels. Despite a lack of clearance of A. fumigatus from the lungs, there was a significant improvement in the rate of survival ($P < 0.001$) and a reduction in the level of pulmonary infarction ($P < 0.05$) in micafungin-treated rabbits. In summary, micafungin demonstrated concentration-dependent and dosage-dependent clearance of C. albicans from persistently neutropenic rabbits with disseminated candidiasis but not of A. fumigatus from persistently neutropenic rabbits with invasive pulmonary aspergillosis.

IT **235114-32-6**, Micafungin
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparative antifungal activities and plasma pharmacokinetics of micafungin (FK463) against disseminated candidiasis and invasive pulmonary aspergillosis in persistently neutropenic rabbits)

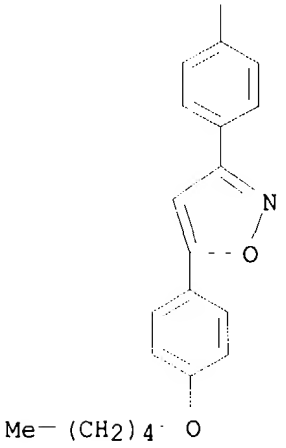
RN 235114-32-6 HCAPLUS

CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]- (9CI) (CA INDEX NAME)

PAGE 1-A



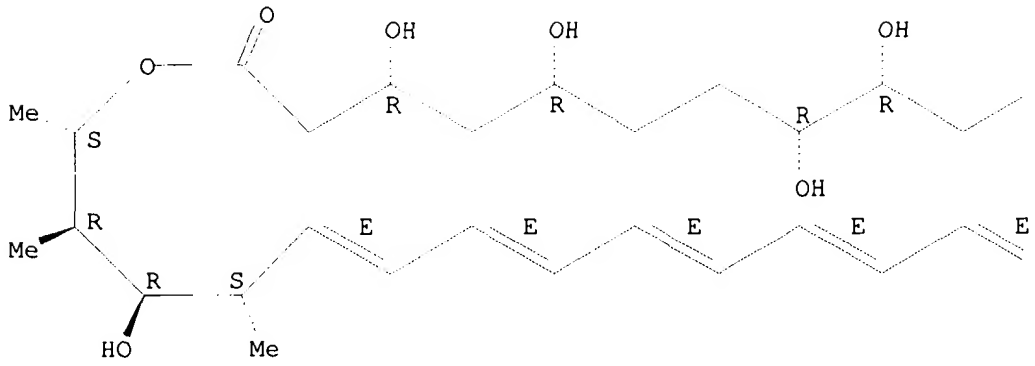
PAGE 2-A



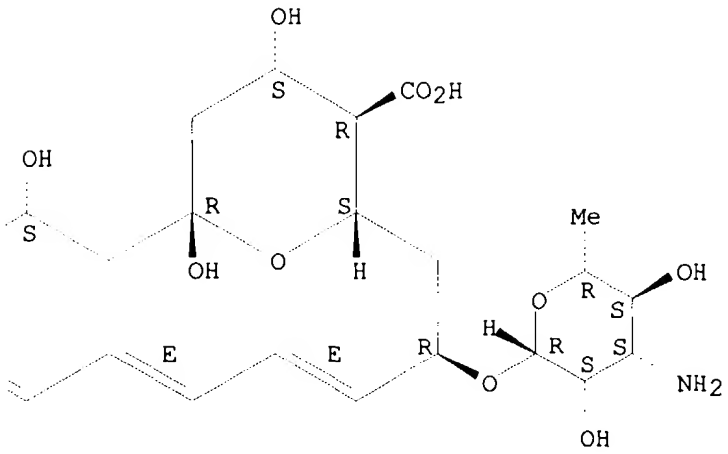
IT **1397-89-3, Amphotericin B**
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparative antifungal activities and plasma pharmacokinetics of micafungin (FK463) against disseminated candidiasis and invasive pulmonary aspergillosis in persistently neutropenic rabbits)
RN 1397-89-3 HCAPLUS
CN Amphotericin B (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



PAGE 1-B



REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 16 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:414514 HCAPLUS
DOCUMENT NUMBER: 137:106402
TITLE: Antifungal susceptibility of Candida biofilms: unique efficacy of **amphotericin B lipid** formulations and

echinocandins

AUTHOR(S): Kuhn, D. M.; George, T.; Chandra, J.; Mukherjee, P. K.; Ghannoum, M. A.

CORPORATE SOURCE: Division of Infectious Diseases, Department of Medicine, and Center for Medical Mycology, Department of Dermatology, University Hospitals of Cleveland and Case Western Reserve University, Cleveland, OH, 44106, USA

SOURCE: Antimicrobial Agents and Chemotherapy (2002), 46(6), 1773-1780
CODEN: AMACCQ; ISSN: 0066-4804

PUBLISHER: American Society for Microbiology

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Biofilms, likely the predominant mode of device-related microbial infection, exhibit resistance to antimicrobial agents. Evidence suggests that Candida biofilms have dramatically reduced susceptibility to antifungal drugs. We examined antifungal susceptibilities of Candida albicans and Candida parapsilosis biofilms grown on a bioprosthetic model. In addition to conventional agents, we determined if new antifungal agents (triazoles, **amphotericin B lipid** formulations, and echinocandins) have activities against Candida biofilms. We also explored effects of preincubation of C. albicans cells with subinhibitory concns. (sub-MICs) of drugs to see if they could modify subsequent biofilm formation. Finally, we used confocal scanning laser microscopy (CSLM) to image planktonic- and biofilm-exposed blastospores to examine drug effects on cell structure. Candida biofilms were formed on silicone elastomer and quantified by tetrazolium and dry weight (DW) assays. Susceptibility testing of **fluconazole, nystatin,** chlorhexidine, terbenafine, **amphotericin B** (AMB), and the triazoles **voriconazole** (VRC) and ravuconazole revealed resistance in all Candida isolates examined when grown as biofilms, compared to planktonic forms. In contrast, **lipid** formulations of AMB (**liposomal** AMB and AMB **lipid** complex [ABLC]) and echinocandins (caspofungin [Casp] and micafungin) showed activity against Candida biofilms. Preincubation of C. albicans cells with sub-MIC levels of antifungals decreased the ability of cells to subsequently form biofilm (measured by DW; $P < 0.0005$). CSLM anal. of planktonic and biofilm-associated blastospores showed treatment with VRC, Casp, and ABLC resulted in morphol. alterations, which differed with each agent. In conclusion, our data show that Candida biofilms show unique susceptibilities to echinocandins and AMB **lipid** formulations.

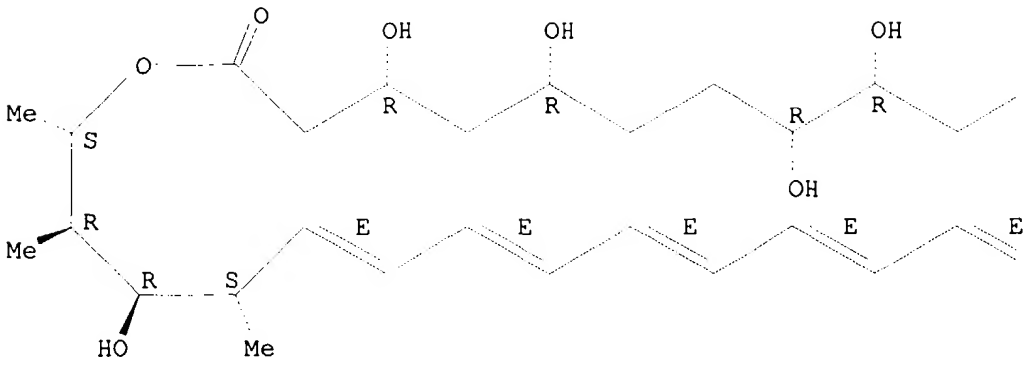
IT **1397-89-3, Amphotericin B**
1400-61-9, Nystatin 86386-73-4,
Fluconazole 137234-62-9, Voriconazole
182760-06-1, Ravuconazole **235114-32-6,** Micafungin
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(**amphotericin B lipid** formulations and echinocandins antifungal effects against Candida biofilms compared with common fungicides)

RN 1397-89-3 HCAPLUS

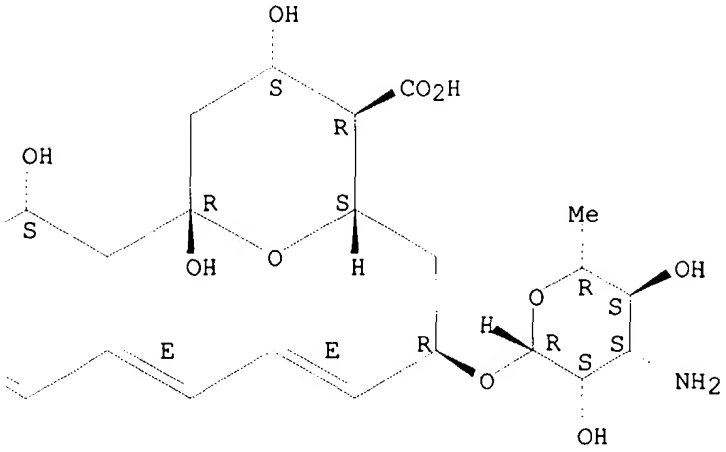
CN Amphotericin B (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A

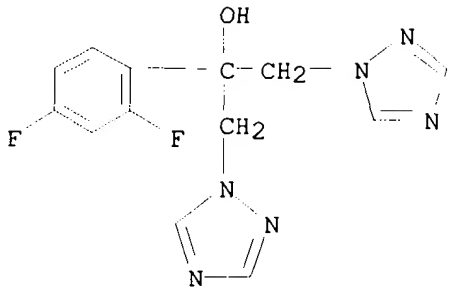


PAGE 1-B



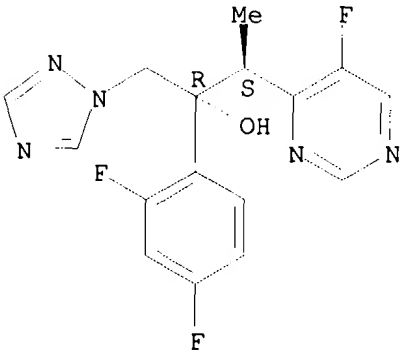
RN 1400-61-9 HCAPLUS
CN Nystatin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 86386-73-4 HCAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)- (9CI) (CA INDEX NAME)



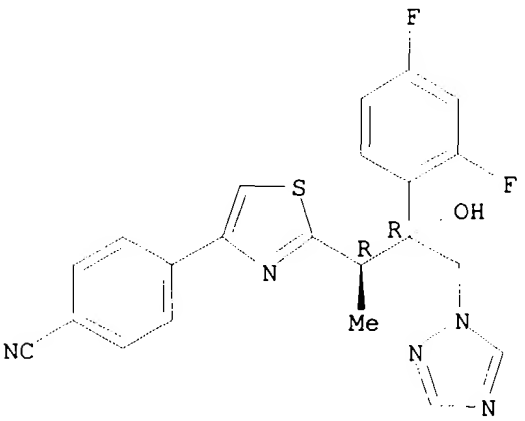
RN 137234-62-9 HCAPLUS
CN 4-Pyrimidineethanol, α-(2,4-difluorophenyl)-5-fluoro-β-methyl-α-(1H-1,2,4-triazol-1-ylmethyl)-, (αR,βS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



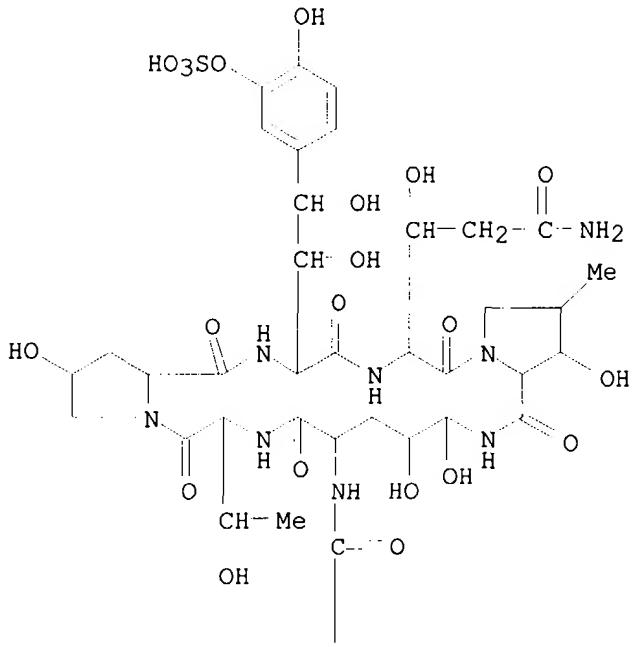
RN 182760-06-1 HCAPLUS
CN Benzonitrile, 4-[2-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-thiazolyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 235114-32-6 HCAPLUS
CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]- (9CI) (CA INDEX NAME)

PAGE 1-A



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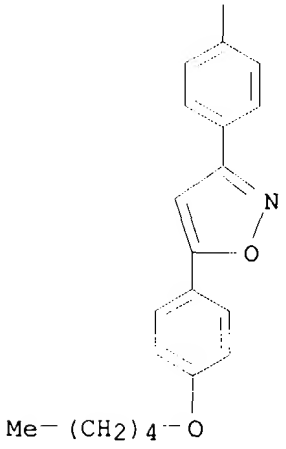


REFERENCE COUNT: 58 THERE ARE 58 CITED REFERENCES AVAILABLE

Searcher : Shears 308-4994

FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

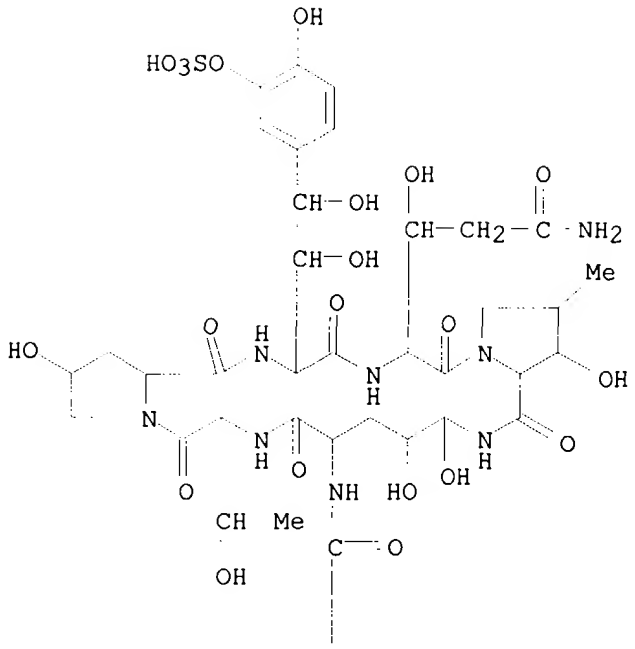
L13 ANSWER 17 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:393657 HCAPLUS
DOCUMENT NUMBER: 138:34
TITLE: Micafungin sodium (FK-463)
AUTHOR(S): Fromtling, Robert A.
CORPORATE SOURCE: Regulatory Affairs-International, Merck Research Laboratories, Rahway, NJ, 07065-0900, USA
SOURCE: *Drugs of Today* (2002), 38(4), 245-257
CODEN: MDACAP; ISSN: 0025-7656
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review. FK-463 (micafungin) represents the latest development candidate in a novel chemical class of echinocandin lipopeptide antifungal compds. This agent has potent in vitro and exptl. in vivo activity against a variety of pathogenic Candida species (yeasts) and Aspergillus fumigatus (filamentous fungus). This compound has favorable pharmacokinetics and a unique mode of action that makes it active against fungal isolates resistant to established antifungal agents, particularly the triazole agent **fluconazole**. Single- and multiple-dose phase I studies in normal human volunteers and phase II clin. trials in patients have been completed, with the compound being generally well tolerated and efficacious against infections caused by Candida and Aspergillus species. Published information on the in vitro and exptl. in vivo activity, exptl. and human pharmacokinetics, and clin. trial data of this new antifungal, echinocandin-like lipopeptide are summarized in this monograph.

IT **208538-73-2**, FK-463
RL: PAC (Pharmacological activity); PKT (Pharmacokinetics); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(echinocandin lipopeptide antifungal FK-463 activity against Aspergillus and Candida)

RN 208538-73-2 HCAPLUS
CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]-, monosodium salt (9CI) (CA INDEX NAME)

PAGE 1-A



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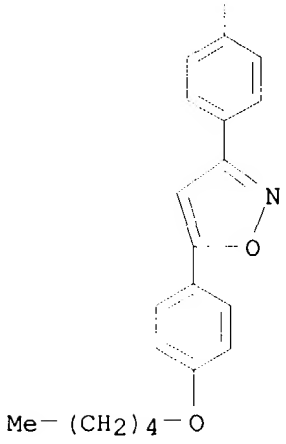

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REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Searcher : Shears 308-4994

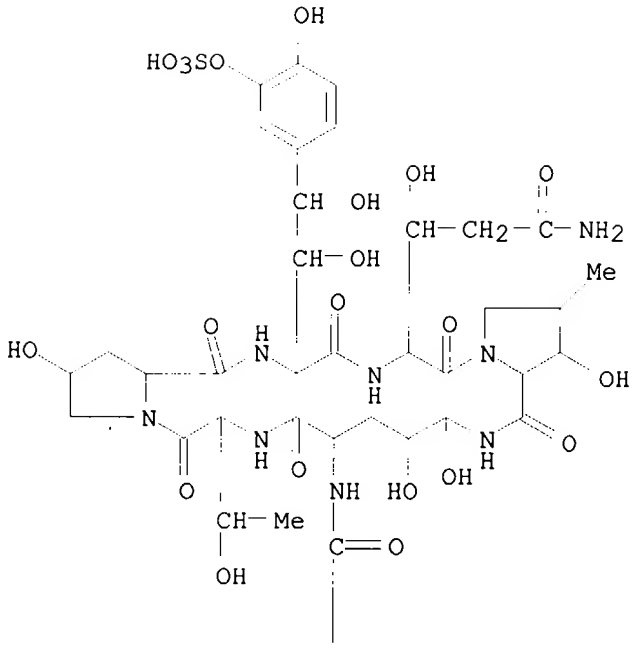
L13 ANSWER 18 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:365727 HCAPLUS
DOCUMENT NUMBER: 137:122114
TITLE: In vitro Activity of FK463, a Novel Lipopeptide Antifungal Agent, against a Variety of Clinically Important Molds
AUTHOR(S): Nakai, T.; Uno, J.; Otomo, K.; Ikeda, F.; Tawara, S.; Goto, T.; Nishimura, K.; Miyaji, M.
CORPORATE SOURCE: Research Center for Pathogenic Fungi and Microbial Toxicoses, Chiba University, Chiba, Japan
SOURCE: Chemotherapy (Basel, Switzerland) (2002), 48(2), 78-81
CODEN: CHTHBK; ISSN: 0009-3157
PUBLISHER: S. Karger AG
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The in vitro antifungal activity of FK463 against a variety of clin. important opportunistic molds was compared with **amphotericin B**, **itraconazole**, and **fluconazole** by the broth microdilution method M27-A specified by the National Committee for Clin. Laboratory Stds. FK463 exhibited potent activity against Aspergillus species, which was superior to those of all other compds. tested. FK463 was also active against the dematiaceous fungi Cladosporium trichoides, Exophiala spinifera, Fonsecaea pedrosoi, and Exophiala dermatitidis except for certain clin. isolates. However, FK463 had no activity against Fusarium solani, Pseudallesheria boydii, and the zygomycetes Absidia corymbifera, Cunninghamella elegans, Rhizopus oryzae, and Rhizopus microsporus var. rhizopodiformis. These results suggest that FK463 has potential utility for the treatment for infections caused by Aspergillus species and dematiaceous fungi.

IT **208538-73-2**, FK463
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vitro antifungal activity of lipopeptide FK463 against pathogenic fungi)

RN 208538-73-2 HCAPLUS
CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]-, monosodium salt (9CI) (CA INDEX NAME)

PAGE 1-A



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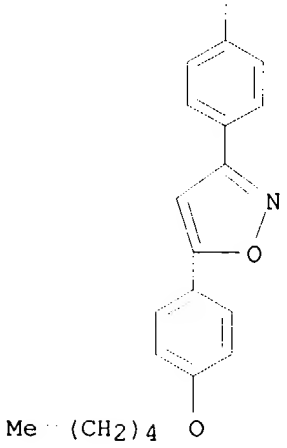


● Na

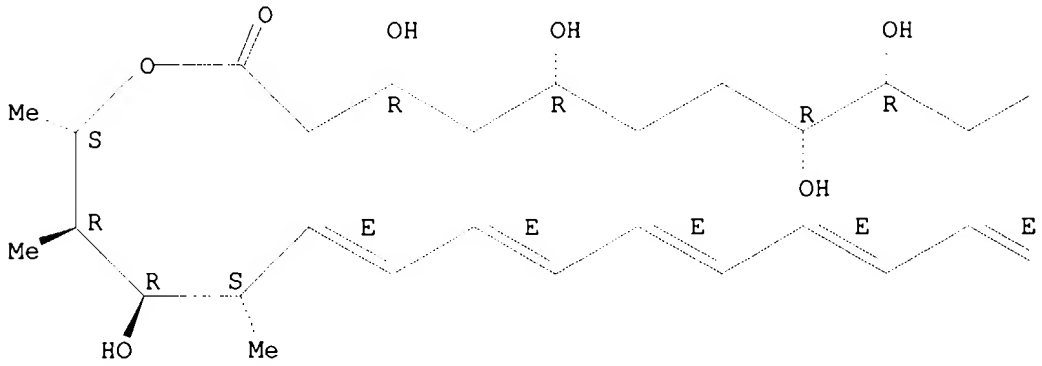
IT **1397-89-3, Amphotericin B**
84625-61-6, Itraconazole 86386-73-4,
Fluconazole
RL: BSU (Biological study, unclassified); THU (Therapeutic use);

BIOL (Biological study); USES (Uses)
(in vitro comparative antifungal activity of lipopeptide FK463 against pathogenic fungi)

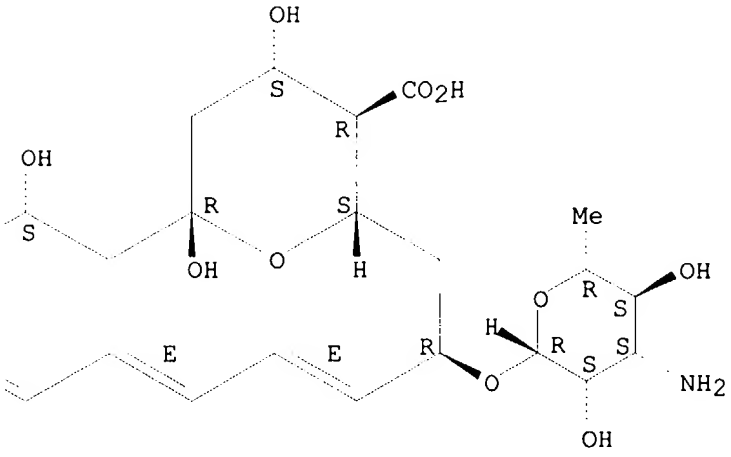
RN 1397-89-3 HCAPLUS
CN Amphotericin B (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A

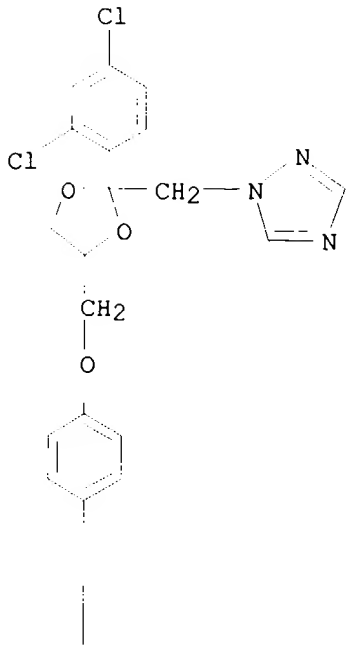


PAGE 1-B



RN 84625-61-6 HCAPLUS
CN 3H-1,2,4-Triazol-3-one, 4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)- (9CI) (CA INDEX NAME)

PAGE 1-A



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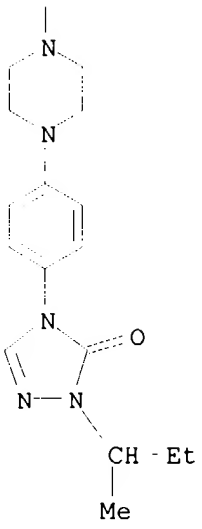
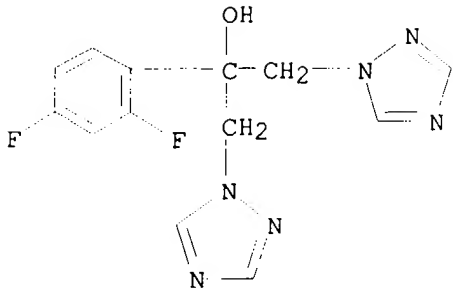


RN 86386-73-4 HCAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 19 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:332011 HCAPLUS
DOCUMENT NUMBER: 136:355482
TITLE: Compositions comprising a polypeptide and an active agent
INVENTOR(S): Piccariello, Thomas; Olon, Lawrence P.; Kirk, Randall J.
PATENT ASSIGNEE(S): New River Pharmaceuticals, Inc., USA
SOURCE: PCT Int. Appl., 98 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002034237	A1	20020502	WO 2001-US26142	20010822
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
AU 2001086599	A5	20020506	AU 2001-86599	20010822
EP 1311242	A1	20030521	EP 2001-966056	20010822
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2000-642820 A 20000822
WO 2001-US26142 W 20010822

AB Claimed are compns. comprising a polypeptide and an active agent covalently attached to the polypeptide and a method for delivery of an active agent to a patient by administering the composition to the patient. The peptide is a homopolymer of a naturally occurring amino acid or a heteropolymer of two or more naturally occurring amino acids. In an example, (Glu)n-cephalexin was prepared from

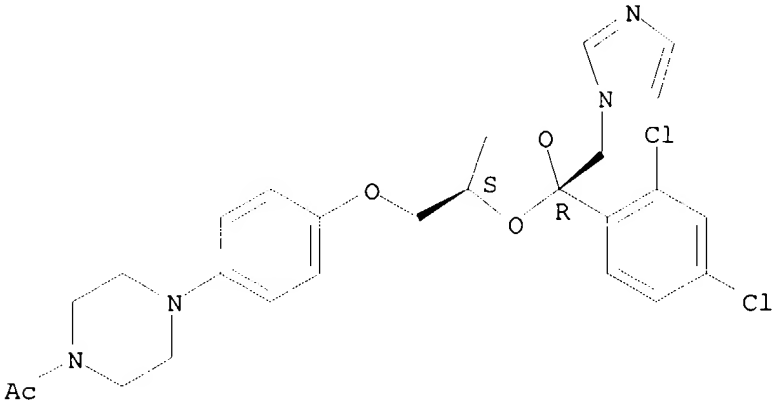
Glu(OBut)NCA and cephalexin hydrochloride.

IT **65277-42-1, Ketoconazole 84625-61-6, Itraconazole 86386-73-4, Fluconazole 137234-62-9, Voriconazole 171228-49-2,** Posaconazole **208538-73-2,** FK 463
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(compns. comprising a polypeptide and an active agent)

RN 65277-42-1 HCAPLUS

CN Piperazine, 1-acetyl-4-[4-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-, rel- (9CI) (CA INDEX NAME)

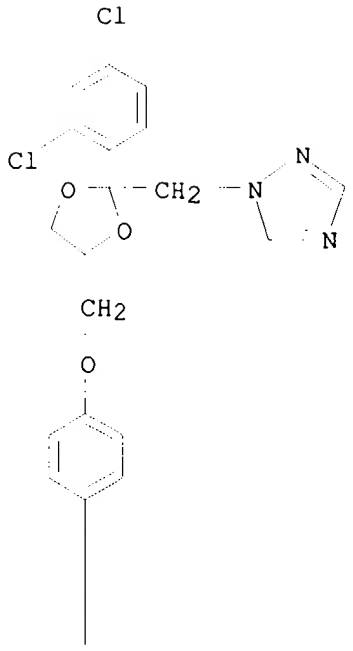
Relative stereochemistry.



RN 84625-61-6 HCAPLUS

CN 3H-1,2,4-Triazol-3-one, 4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)- (9CI) (CA INDEX NAME)

PAGE 1-A



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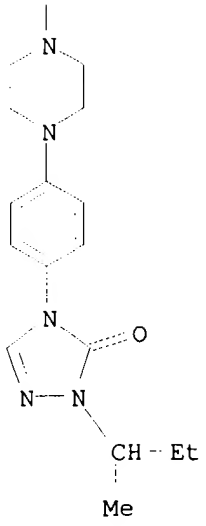
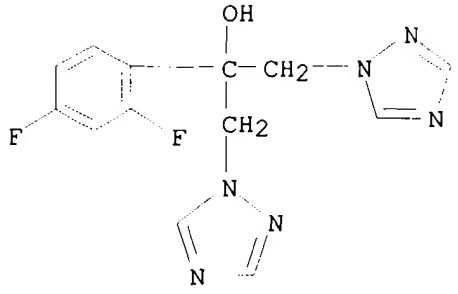
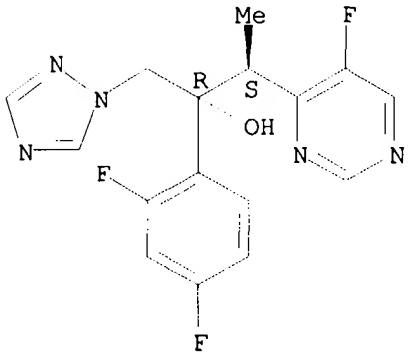


RN 86386-73-4 HCAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)- (9CI) (CA INDEX NAME)



RN 137234-62-9 HCAPLUS
CN 4-Pyrimidineethanol, α-(2,4-difluorophenyl)-5-fluoro-β-methyl-α-(1H-1,2,4-triazol-1-ylmethyl)-, (αR,βS)- (9CI) (CA INDEX NAME)

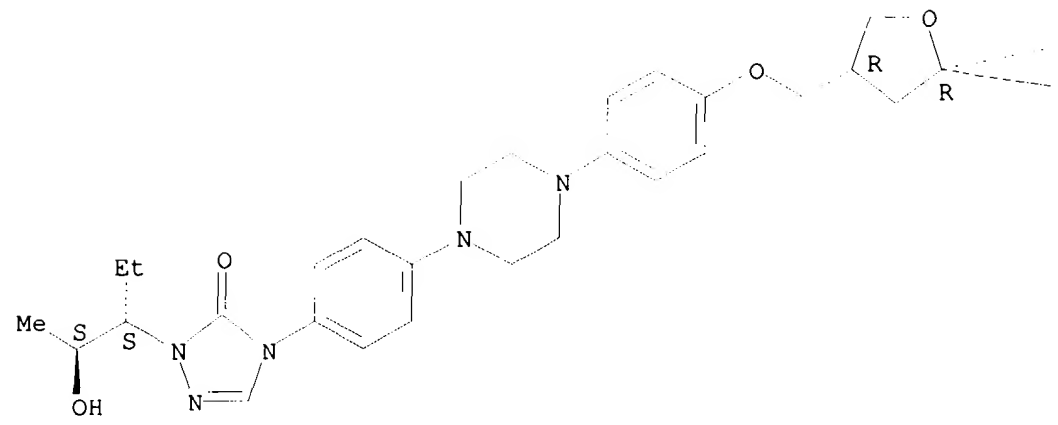
Absolute stereochemistry.



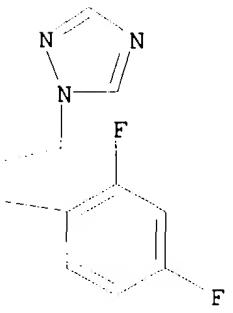
RN 171228-49-2 HCAPLUS
CN D-threo-Pentitol, 2,5-anhydro-1,3,4-trideoxy-2-C-(2,4-difluorophenyl)-4-[[4-[4-[4-[1-[(1S,2S)-1-ethyl-2-hydroxypropyl]-1,5-dihydro-5-oxo-4H-1,2,4-triazol-4-yl]phenyl]-1-piperazinyl]phenoxy]methyl]-1-(1H-1,2,4-triazol-1-yl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

PAGE 1-A

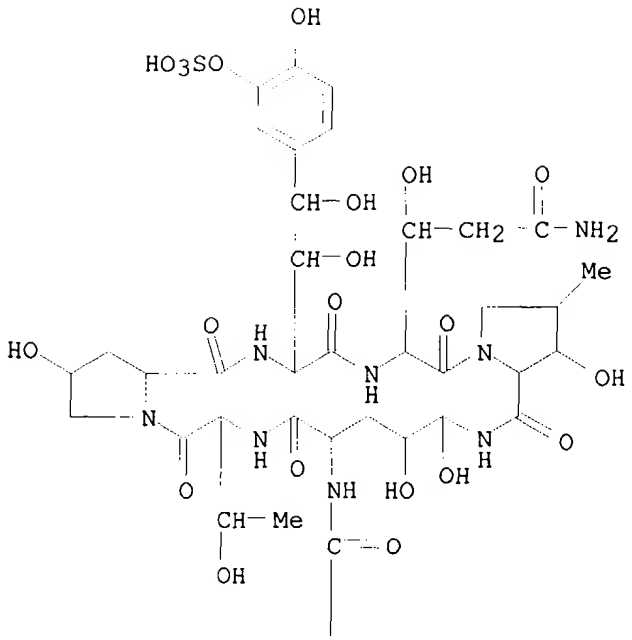


PAGE 1-B



RN 208538-73-2 HCAPLUS
CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]-, monosodium salt (9CI) (CA INDEX NAME)

PAGE 1-A



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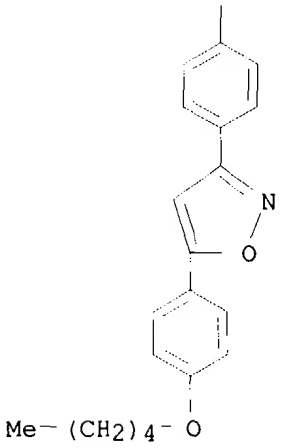

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REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Searcher : Shears 308-4994

L13 ANSWER 20 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:888799 HCAPLUS
DOCUMENT NUMBER: 136:99004
TITLE: Effect of the growth medium on the in vitro antifungal activity of micafungin (FK-463) against clinical isolates of Candida dubliniensis
AUTHOR(S): Muller, F.-M. C.; Kurzai, O.; Hacker, J.; Frosch, M.; Muhlschlegel, F.
CORPORATE SOURCE: Department of Paediatrics, Institute for Molecular Biology of Infection, University of Wurzburg, Wurzburg, D-97080, Germany
SOURCE: Journal of Antimicrobial Chemotherapy (2001), 48(5), 713-715
CODEN: JACHDX; ISSN: 0305-7453
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

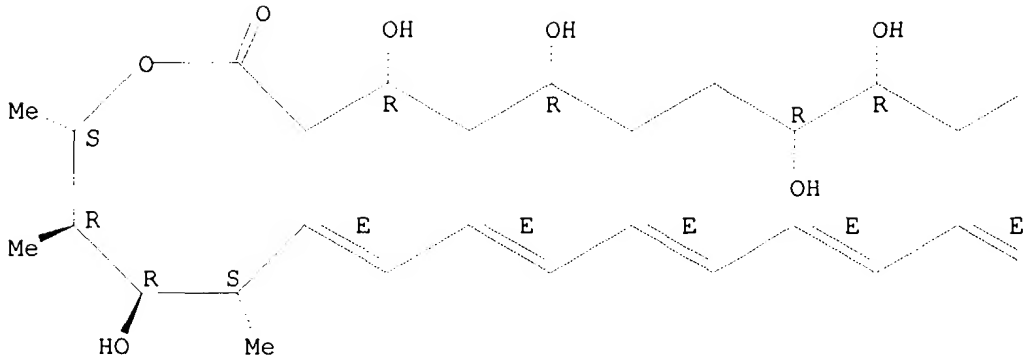
AB Micafungin (FK-463), a member of the new candin family of antifungal agents, was highly active against clin. isolates of Candida albicans and Candida dubliniensis. The in vitro activity of micafungin suggested that it was more potent than **fluconazole**, **flucytosine**, **amphotericin B**, or **voriconazole** against C. albicans, and comparable or moderately less effective against C. dubliniensis isolates when high-resolution medium (HR) was used. Lower MICs of micafungin were recorded when RPMI 2% or AM3 2% media were used, indicating an influence of the growth medium on the MIC.

IT **1397-89-3**, **Amphotericin B**
2022-85-7, **Flucytosine** **86386-73-4**,
Fluconazole **137234-62-9**, **Voriconazole**
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vitro antifungal activity against Candida dubliniensis and C. albicans affected by growth medium)

RN 1397-89-3 HCAPLUS
CN Amphotericin B (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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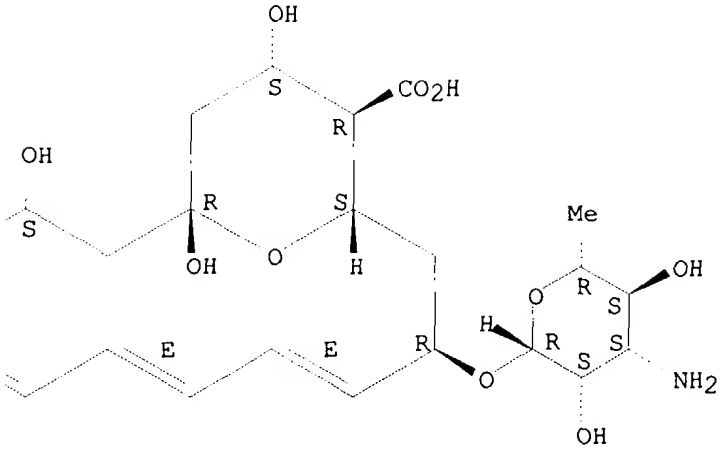
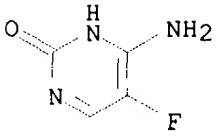
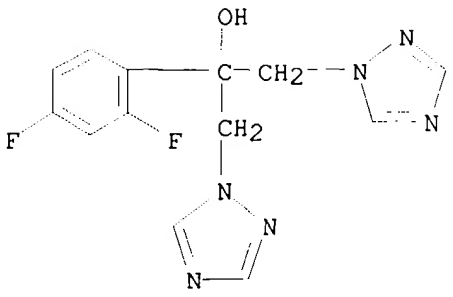


RN 2022-85-7 HCAPLUS
CN 2(1H)-Pyrimidinone, 4-amino-5-fluoro- (9CI) (CA INDEX NAME)



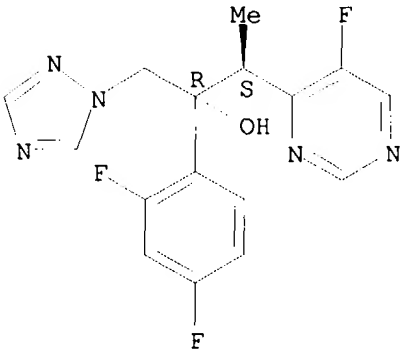
RN 86386-73-4 HCAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-

(1H-1,2,4-triazol-1-ylmethyl)- (9CI) (CA INDEX NAME)



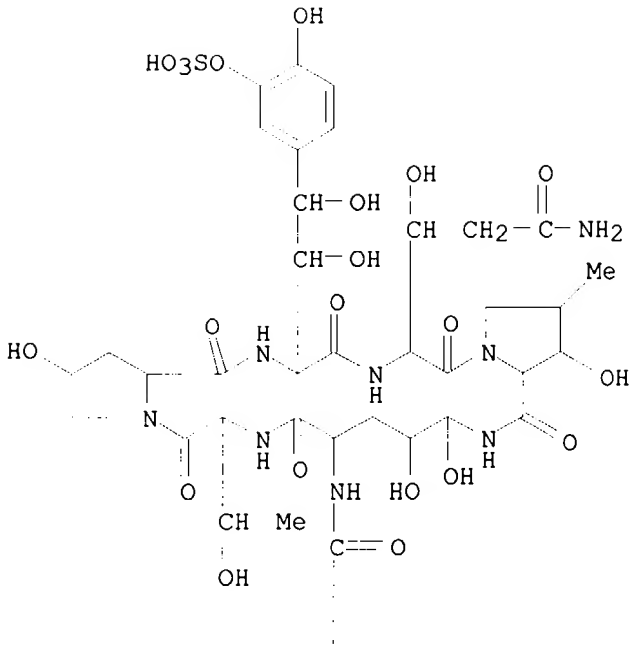
RN 137234-62-9 HCAPLUS
CN 4-Pyrimidineethanol, α-(2,4-difluorophenyl)-5-fluoro-β-methyl-α-(1H-1,2,4-triazol-1-ylmethyl)-, (αR,βS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



IT **235114-32-6**, Micafungin
RL: BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vitro antifungal activity of micafungin (FK-463) against Candida dubliniensis and C. albicans affected by growth medium)
RN 235114-32-6 HCAPLUS
CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]- (9CI) (CA INDEX NAME)

PAGE 1-A



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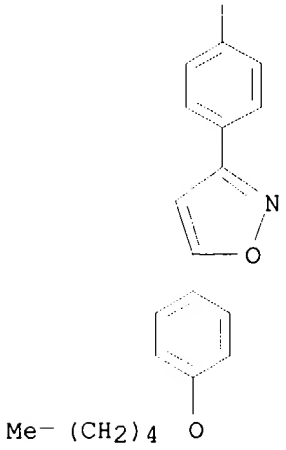


REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 21 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:861505 HCAPLUS
DOCUMENT NUMBER: 134:27477
TITLE: Antifungal combination use of lipopeptide with

other agents

INVENTOR(S): Ikeda, Fumiaki; Otomo, Kazumi; Wakai, Yosimi; Matsumoto, Satoru
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan

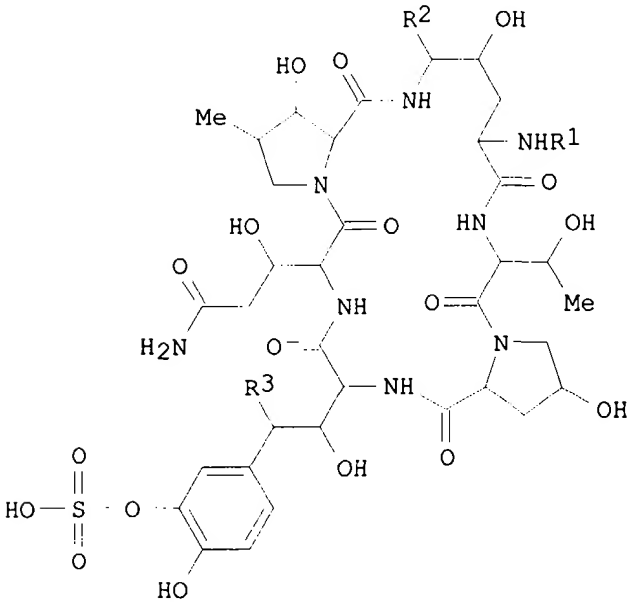
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000072865	A2	20001207	WO 2000-JP3340	20000524
WO 2000072865	A3	20010510		
W: JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1180038	A2	20020220	EP 2000-929859	20000524
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2003527314	T2	20030916	JP 2000-620974	20000524

PRIORITY APPLN. INFO.: AU 1999-663 A 19990531
WO 2000-JP3340 W 20000524

OTHER SOURCE(S): MARPAT 134:27477

GI



I

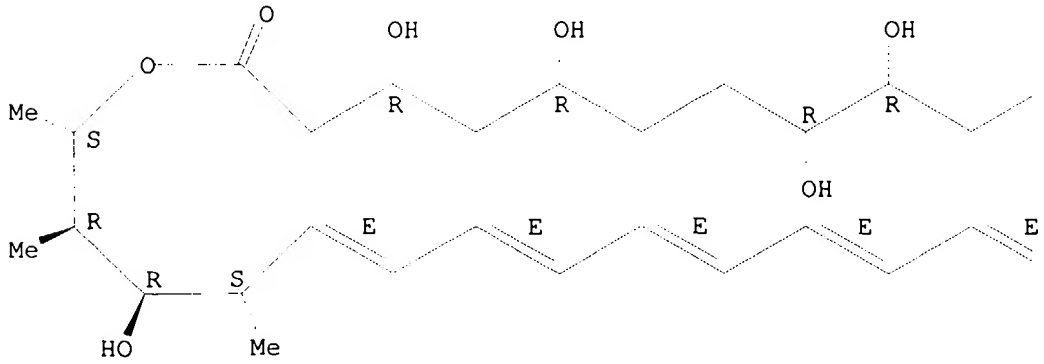
AB There is described antifungal combination use of known antifungal agents such as the azoles or polyenes in combination with a lipopeptide compound antifungal agent. More particularly, the

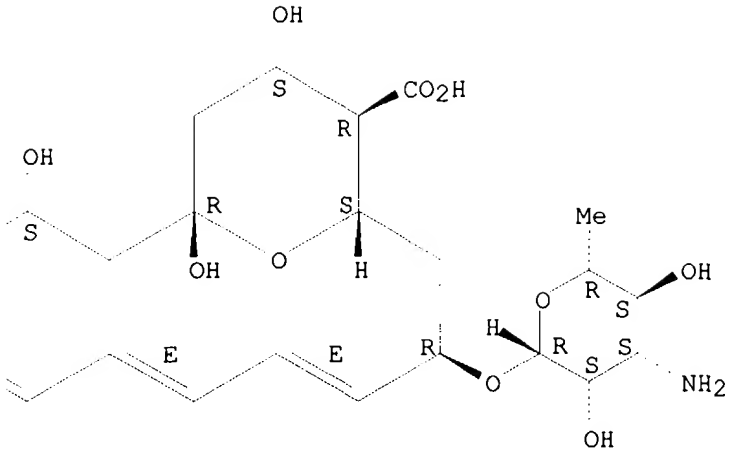
invention relates to antifungal combination use of azoles such as **fluconazole, voriconazole, itraconazole, ketoconazole, miconazole, ER 30346** and **SCH 56592**; polyenes such as **amphotericin B, nystatin, liposomal** and **lipid** forms thereof such as Abelcet, AmBisome and Amphocil; purine or pyrimidine nucleotide inhibitors such as **flucytosine**; or polyoxins such as nikkomycins, in particular nikkomycin Z or **nikkomycin X**; other chitin inhibitors; elongation factor inhibitors such as **sordarin** and analogs thereof; mannan inhibitors such as **predamycin**, bactericidal/permeability-inducing (BPI) protein products such as XMP.97 or XMP.127; or complex carbohydrate antifungal agents such as CAN-296; with a lipopeptide compound (I: R1 = acyl and R2 and R3 = H or OH) as described herein.

IT **1397-89-3, Amphotericin B 1400-61-9, Nystatin 2022-85-7, Flucytosine 11076-17-8, Sordarin 11076-17-8D, Sordarin**, analogs **22916-47-8 , Miconazole 65277-42-1, Ketoconazole 72864-26-7, Nikkomycin X 84625-61-6, Itraconazole 86386-73-4, Fluconazole 137234-62-9, Voriconazole 171228-49-2, SCH 56592 182760-06-1, ER 30346 235114-32-6D**, isomers **312268-90-9, Predamycin**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antifungal combination use of lipopeptide with other agents such as azoles and polyenes)

RN 1397-89-3 HCAPLUS
CN Amphotericin B (8CI, 9CI) (CA INDEX NAME)

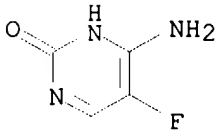
Absolute stereochemistry.
Double bond geometry as shown.





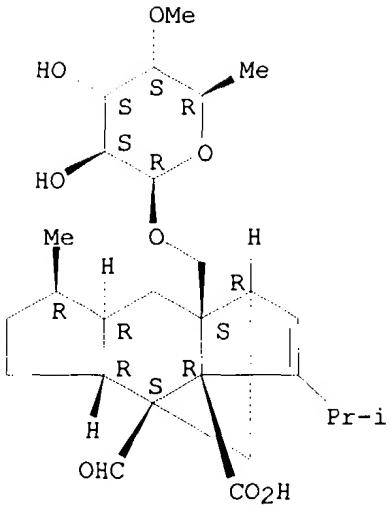
RN 1400-61-9 HCAPLUS
CN Nystatin (8CI, 9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
RN 2022-85-7 HCAPLUS
CN 2(1H)-Pyrimidinone, 4-amino-5-fluoro- (9CI) (CA INDEX NAME)



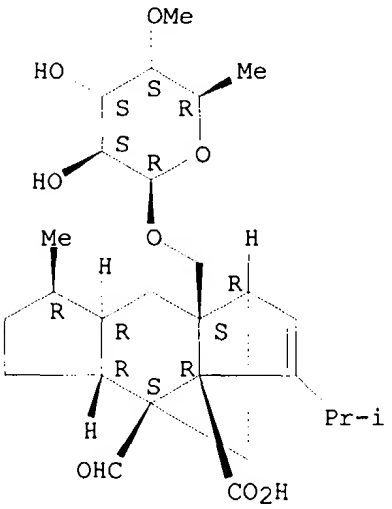
RN 11076-17-8 HCAPLUS
CN 1,4-Methano-s-indacene-3a(1H)-carboxylic acid, 8a-[[(6-deoxy-4-O-methyl-β-D-altropyranosyl)oxy]methyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-, (1R,3aR,4S,4aR,7R,7aR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

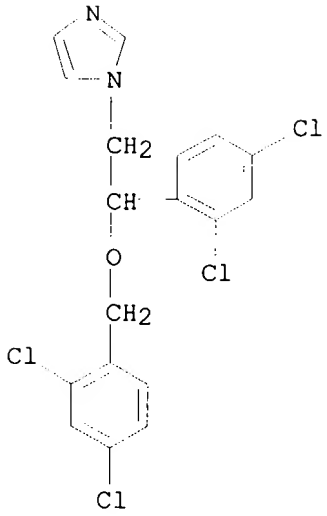


RN 11076-17-8 HCAPLUS
CN 1,4-Methano-s-indacene-3a(1H)-carboxylic acid, 8a-[[(6-deoxy-4-O-methyl-β-D-altropyranosyl)oxy]methyl]-4-formyl-4,4a,5,6,7,7a,8,8a-octahydro-7-methyl-3-(1-methylethyl)-, (1R,3aR,4S,4aR,7R,7aR,8aS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

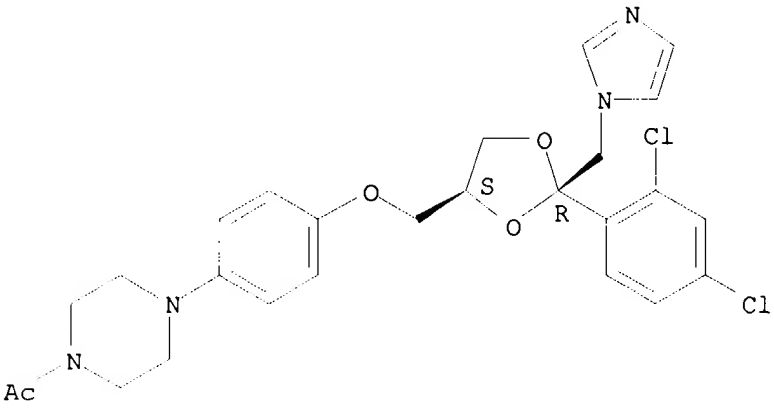


RN 22916-47-8 HCAPLUS
CN 1H-Imidazole, 1-[2-(2,4-dichlorophenyl)-2-[(2,4-dichlorophenyl)methoxy]ethyl]- (9CI) (CA INDEX NAME)

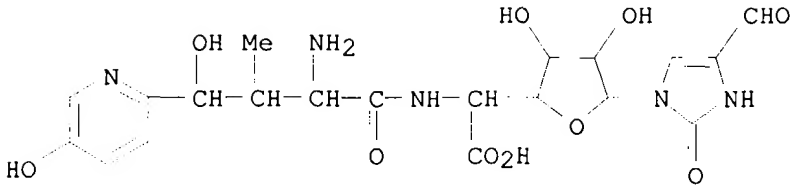


RN 65277-42-1 HCAPLUS
CN Piperazine, 1-acetyl-4-[4-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-, rel- (9CI) (CA INDEX NAME)

Relative stereochemistry.

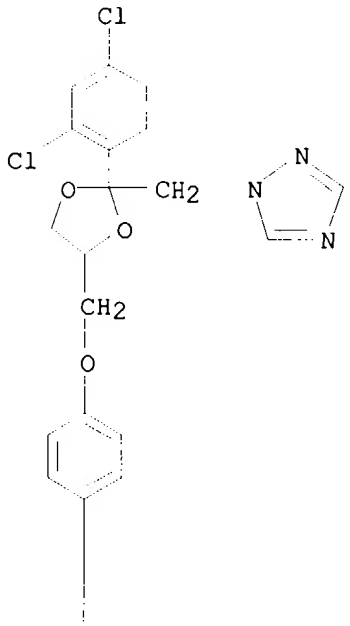


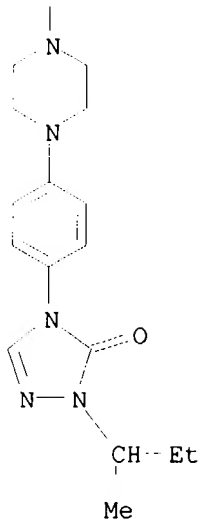
RN 72864-26-7 HCAPLUS
CN β-D-Allofuranuronic acid, 5-[[(2S,3S,4S)-2-amino-4-hydroxy-4-(5-hydroxy-2-pyridinyl)-3-methyl-1-oxobutyl]amino]-1,5-dideoxy-1-(4-formyl-2,3-dihydro-2-oxo-1H-imidazol-1-yl)- (9CI) (CA INDEX NAME)



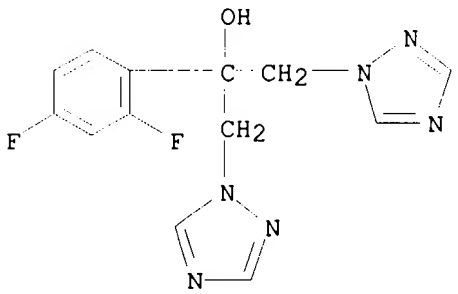
RN 84625-61-6 HCAPLUS
CN 3H-1,2,4-Triazol-3-one, 4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)- (9CI) (CA INDEX NAME)

PAGE 1-A



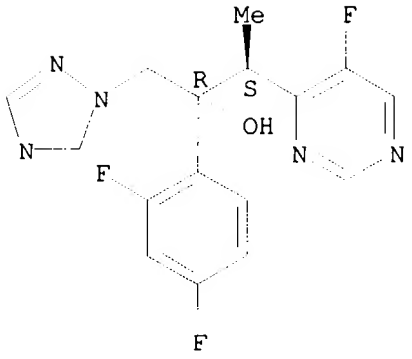


RN 86386-73-4 HCAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)- (9CI) (CA INDEX NAME)



RN 137234-62-9 HCAPLUS
CN 4-Pyrimidineethanol, α-(2,4-difluorophenyl)-5-fluoro-β-methyl-α-(1H-1,2,4-triazol-1-ylmethyl)-, (αR,βS)-(9CI) (CA INDEX NAME)

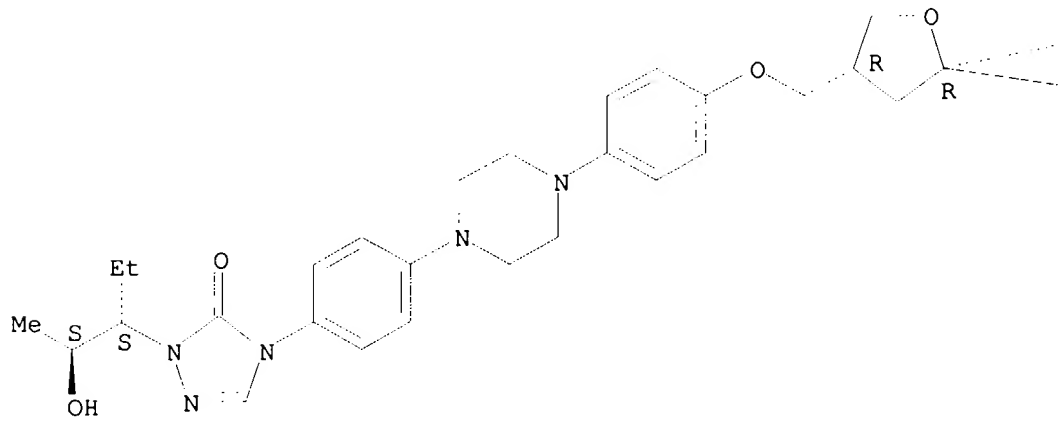
Absolute stereochemistry.

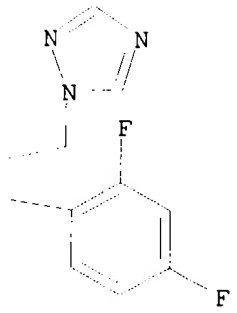


RN 171228-49-2 HCAPLUS
CN D-threo-Pentitol, 2,5-anhydro-1,3,4-trideoxy-2-C-(2,4-difluorophenyl)-4-[[4-[4-[4-[1-[(1S,2S)-1-ethyl-2-hydroxypropyl]-1,5-dihydro-5-oxo-4H-1,2,4-triazol-4-yl]phenyl]-1-piperazinyl]phenoxy]methyl]-1-(1H-1,2,4-triazol-1-yl)- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).

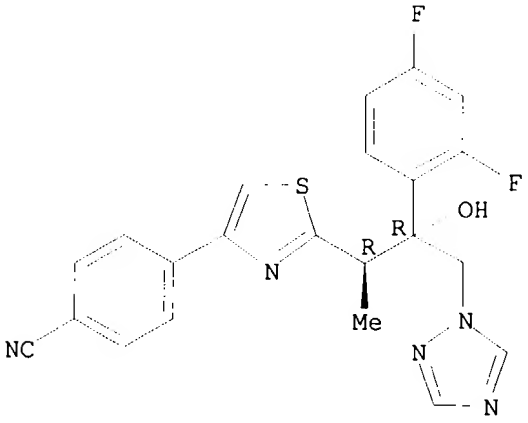
PAGE 1-A





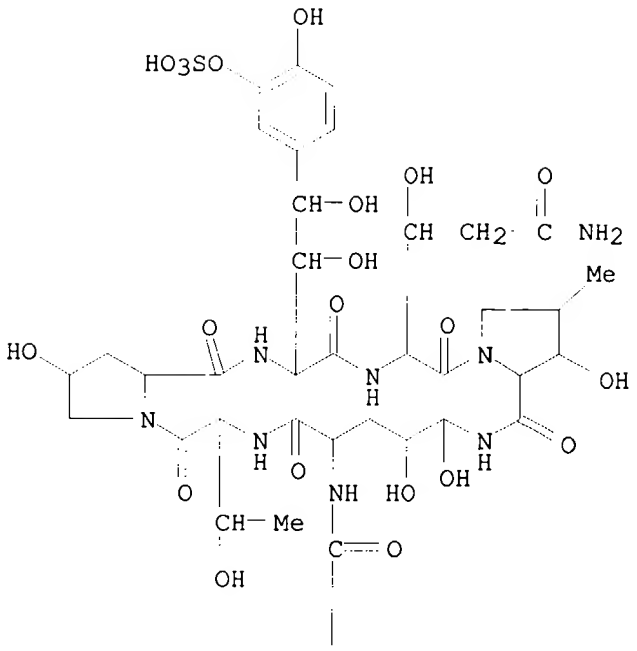
RN 182760-06-1 HCAPLUS
CN Benzonitrile, 4-[2-[(1R,2R)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1H-1,2,4-triazol-1-yl)propyl]-4-thiazolyl]- (9CI) (CA INDEX NAME)

Absolute stereochemistry. Rotation (-).



RN 235114-32-6 HCAPLUS
CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]- (9CI) (CA INDEX NAME)

PAGE 1-A



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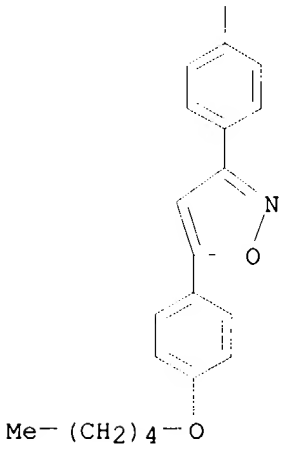


RN 312268-90-9 HCAPLUS
CN Predamycin (9CI) (CA INDEX NAME)

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***

L13 ANSWER 22 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:780063 HCAPLUS
DOCUMENT NUMBER: 134:53729

TITLE:	In vitro antifungal activity of a novel lipopeptide antifungal agent, FK463, against various fungal pathogens
AUTHOR(S):	Uchida, K.; Nishiyama, Y.; Yokota, N.; Yamaguchi, H.
CORPORATE SOURCE:	Teikyo University Institute of Medical Mycology, Tokyo, 192-0395, Japan
SOURCE:	Journal of Antibiotics (2000), 53(10), 1175-1181 CODEN: JANTAJ; ISSN: 0021-8820
PUBLISHER:	Japan Antibiotics Research Association
DOCUMENT TYPE:	Journal
LANGUAGE:	English

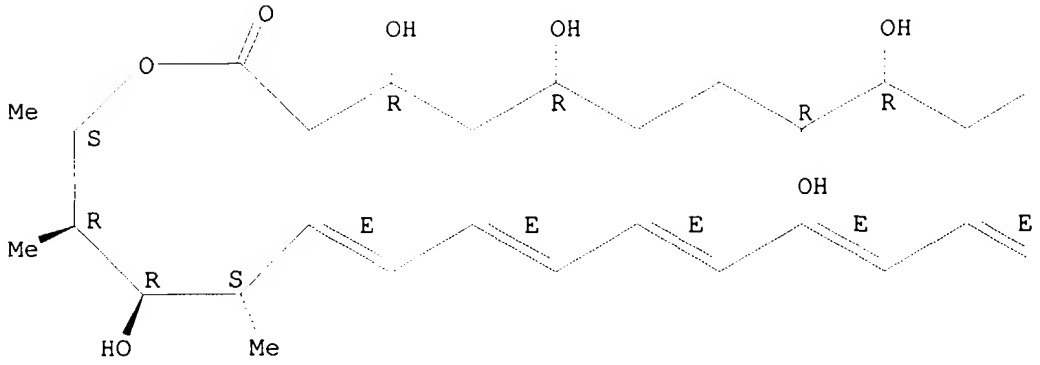
AB The antifungal activities of FK463 against various pathogenic fungi were tested by standard broth microdilution methods, and compared with the activities of five currently available antifungal agents; viz., **fluconazole** (FLCZ), **itraconazole, miconazole, amphotericin B** and **flucytosine**. Fourteen clin. isolates of Candida albicans categorized as FLCZ susceptible, FLCZ susceptible-dose dependent and FLCZ resistant were similarly susceptible to FK463 with geometric (GM) MIC values of 0.010, 0.011 and 0.015 μg/mL, resp. All of 17 clin. isolates of Aspergillus fumigatus were inhibited by FK463 at 0.0078 μg/mL or lower concns. The antifungal activity of FK463 against a wider range of medically important yeasts and filamentous fungi were studied using stock fungal strains. While Cryptococcus, Trichosporon, Fusarium, Pseudallescheria and Alternaria species or zygomycetes were scarcely or not inhibited by 16 μg/mL of FK463, two Candida species (C. albicans, C. glabrata), as well as all species of Aspergillus, Paecilomyces and Penicillium, were highly susceptible with GM-MICs of 0.008 μg/mL. The other fungal species including several non-albicans Candida were less susceptible with GM-MICs ranging between 0.016 and 2 μg/mL. MICs of the reference drugs were within the range thus previously reported. These results suggest that FK463 be of use in the treatment of serious fungal infections.

IT **1397-89-3, Amphotericin B**
2022-85-7, Flucytosine. 22916-47-8, Miconazole 84625-61-6, Itraconazole
86386-73-4, Fluconazole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vitro antifungal activity of FK463 comparison to)

RN 1397-89-3 HCAPLUS
CN Amphotericin B (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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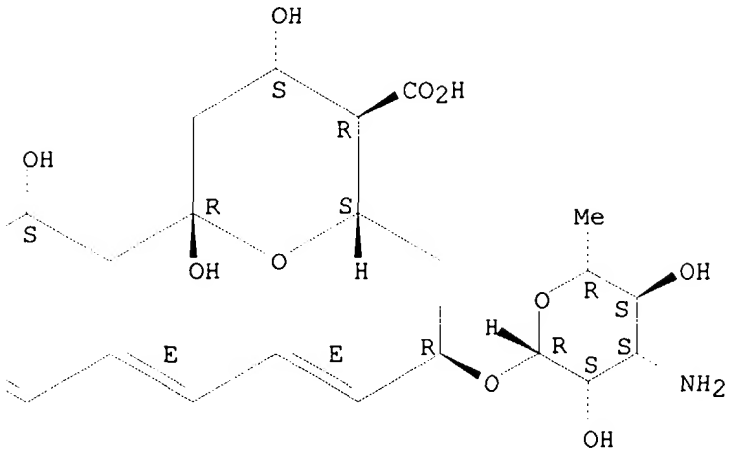
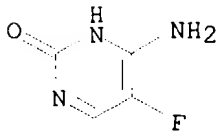
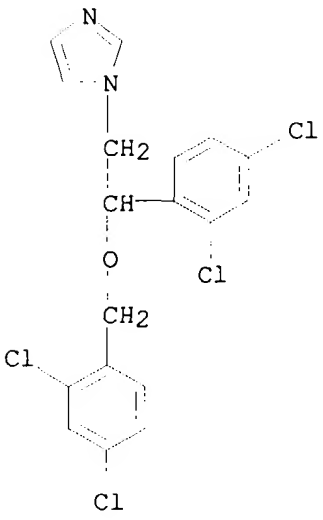


RN 2022-85-7 HCAPLUS
CN 2(1H)-Pyrimidinone, 4-amino-5-fluoro- (9CI) (CA INDEX NAME)



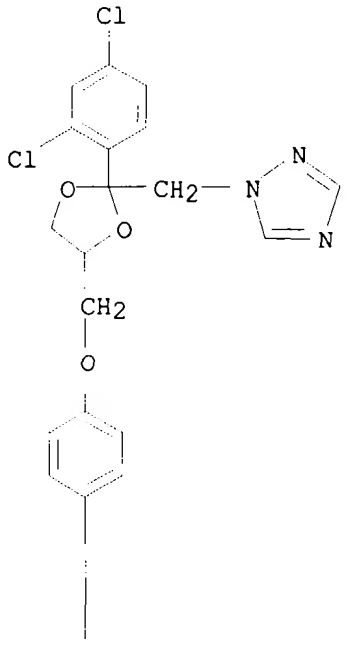
RN 22916-47-8 HCAPLUS
CN 1H-Imidazole, 1-[2-(2,4-dichlorophenyl)-2-[(2,4-

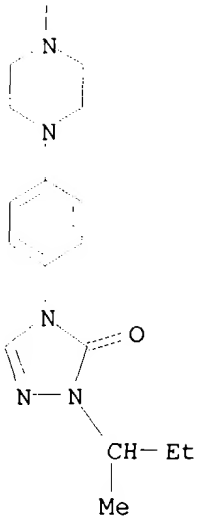
dichlorophenyl)methoxy]ethyl]- (9CI) (CA INDEX NAME)



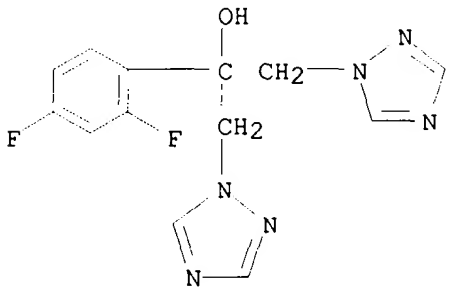
RN 84625-61-6 HCAPLUS
CN 3H-1,2,4-Triazol-3-one, 4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)- (9CI) (CA INDEX NAME)

PAGE 1-A



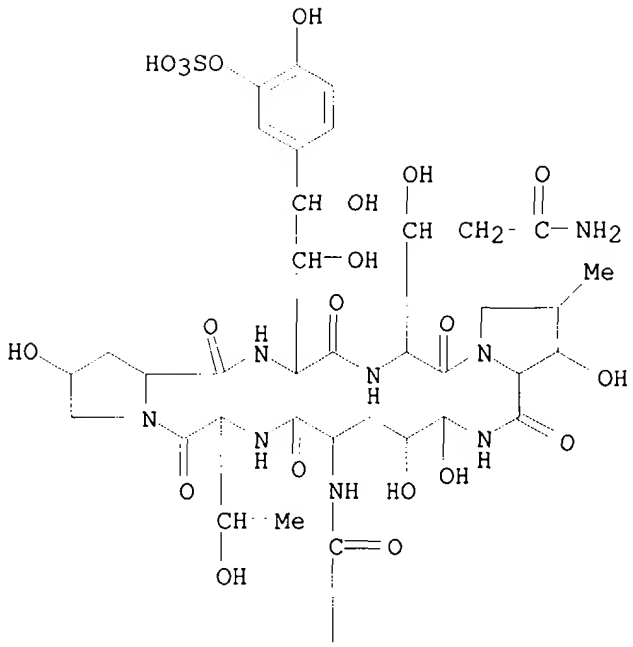


RN 86386-73-4 HCAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)- (9CI) (CA INDEX NAME)



IT **208538-73-2**, FK463
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vitro antifungal activity of the novel lipopeptide antifungal agent FK463 against various fungal pathogens)
RN 208538-73-2 HCAPLUS
CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]-, monosodium salt (9CI) (CA INDEX NAME)

PAGE 1-A



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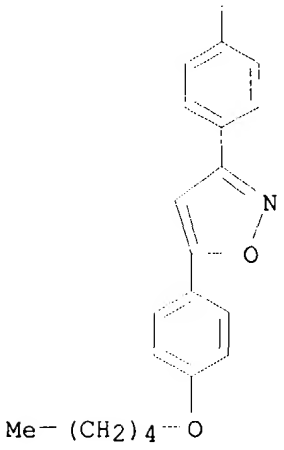

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REFERENCE COUNT: 11 THERE ARE 11 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

Searcher : Shears 308-4994

L13 ANSWER 23 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:689768 HCAPLUS
DOCUMENT NUMBER: 133:346964
TITLE: In vitro antifungal activity of FK463, a new water-soluble echinocandin-like lipopeptide
AUTHOR(S): Mikamo, Hiroshige; Sato, Yasumasa; Tamaya, Teruhiko
CORPORATE SOURCE: Department of Obstetrics and Gynaecology, School of Medicine, Gifu University, Gifu City, 500-8705, Japan
SOURCE: Journal of Antimicrobial Chemotherapy (2000), 46(3), 485-487
CODEN: JACHDX; ISSN: 0305-7453
PUBLISHER: Oxford University Press
DOCUMENT TYPE: Journal
LANGUAGE: English

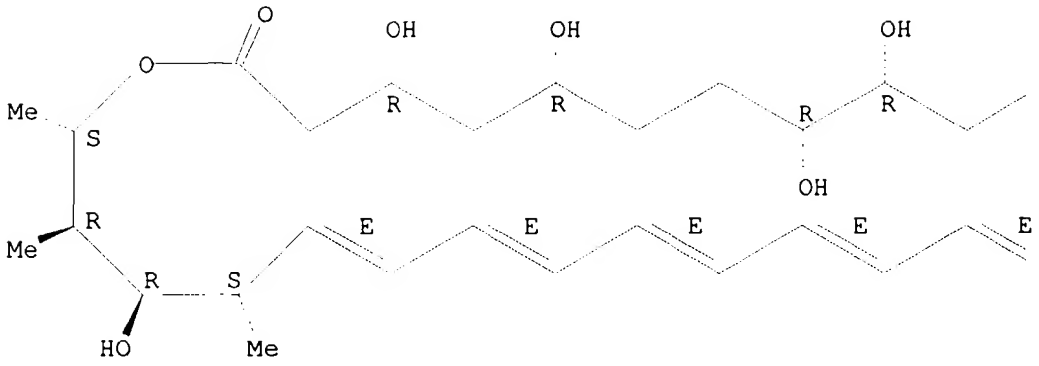
AB The antifungal activity of FK463 against 72 recent clin. isolates of Candida albicans (24), Candida glabrata (17), Candida tropicalis (11), Candida krusei (8) and Candida parapsilosis (12) was compared with those of **amphotericin B**, **fluconazole** and **itraconazole** by means of a broth microdilution method specified by the National Committee for Clin. Laboratory Stds. (NCCLS) document M27-A. The lowest drug concentration at which 90% of the population was inhibited (MIC90) of FK463 against C. albicans, C. glabrata, C. tropicalis, C. krusei and C. parapsilosis was 0.0156, 0.0156, 0.0313, 0.125 and 1 mg/L, resp. FK463 exhibited broad-spectrum activity against clin. important Candida spp. (MIC range ≤0.0039-2 mg/L), and its MICs for such fungi were lower than those of other antifungal agents tested. The min. fungicidal concns. for Candida spp. did not differ by more than two-fold from the MICs. Results from pre-clin. evaluations performed to date indicate that FK463 should be a potent parenteral antifungal agent.

IT **1397-89-3, Amphotericin B**
84625-61-6, Itraconazole 86386-73-4,
Fluconazole 208538-73-2, FK463
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(antifungal activity of the echinochandin like lipopeptide FK463)

RN 1397-89-3 HCAPLUS
CN Amphotericin B (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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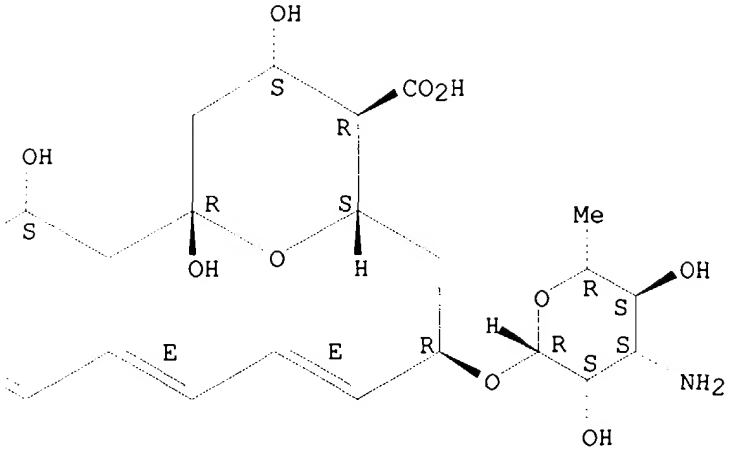

RN 84625-61-6 HCAPLUS
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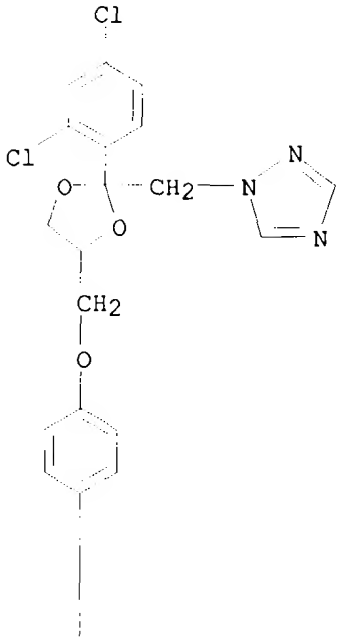
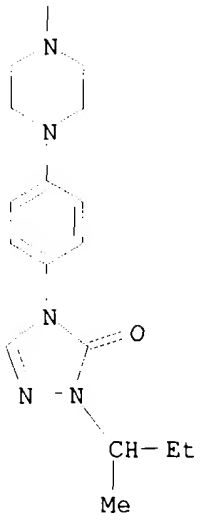
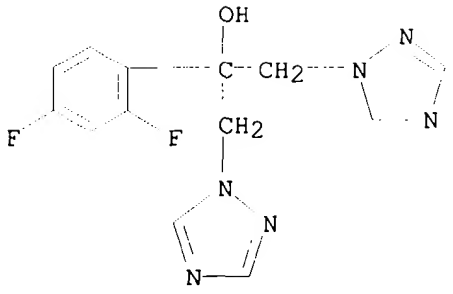
PAGE 1-A



PAGE 2-A

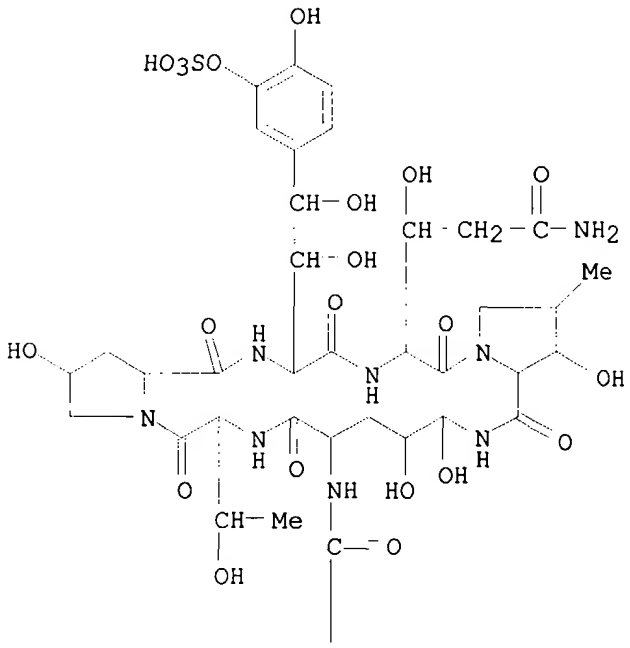


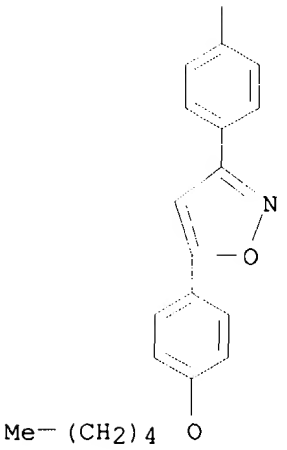
RN 86386-73-4 HCAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)- (9CI) (CA INDEX NAME)



RN 208538-73-2 HCAPLUS
CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]-, monosodium salt (9CI) (CA INDEX NAME)

PAGE 1-A





REFERENCE COUNT: 7 THERE ARE 7 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

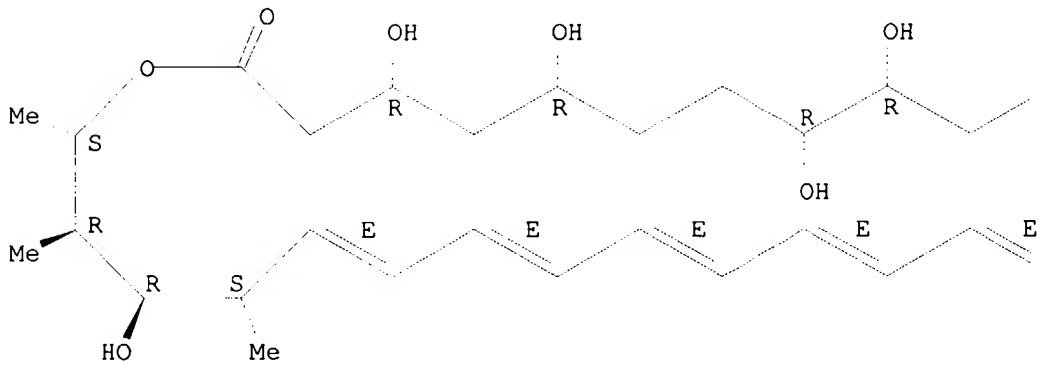
L13 ANSWER 24 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:587949 HCAPLUS
DOCUMENT NUMBER: 134:50854
TITLE: New approaches to systemic antifungal therapy: case studies of AmBisome and FK463
AUTHOR(S): Bekersky, Ihor; Buell, Donald; Tomishima, Masaki; Maki, Katsuyuki; Lawrence, Ira; Fielding, Robert M.
CORPORATE SOURCE: Fujisawa Healthcare, Inc., Deerfield, IL, 60015, USA
SOURCE: Recent Research Developments in Antimicrobial Agents & Chemotherapy (1999), 3(Pt. 2), 407-413 CODEN: RDACFH
PUBLISHER: Research Signpost
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 45 refs. Recent increases in the number of potentially life-threatening systemic fungal infections in immunocompromised patients have made the development of improved antifungal therapies more urgent. Current treatments, including **amphotericin B** and the azoles, suffer from lack of broad-spectrum fungicidal action and/or undesirable toxicities. In this review, two novel but different antifungal prepns. are compared to illustrate the diversity in current approaches to antifungal therapy. A semi-systemic echinicandin analog (FK463) is the result of effortes to develop compds. that inhibit specific biochem. targets found in fungal cells. A **liposomal** formulation of **amphotericin B** (AmBisome) demonstrates the ability of advanced drug delivery systems to improve the safety profile of a toxic, but otherwise effective drug.

IT **1397-89-3**, AmBisome **208538-73-2**, FK463
RL: ADV (Adverse effect, including toxicity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(AmBisome and FK463 antifungals and new approaches to systemic antifungal therapy)
RN 1397-89-3 HCAPLUS
CN Amphotericin B (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A



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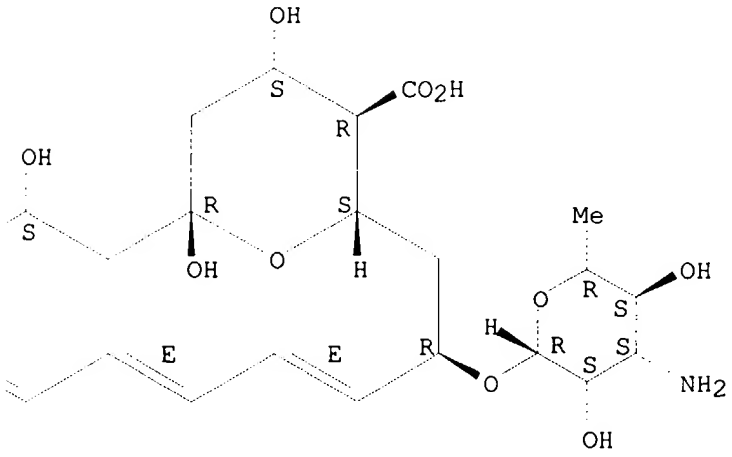

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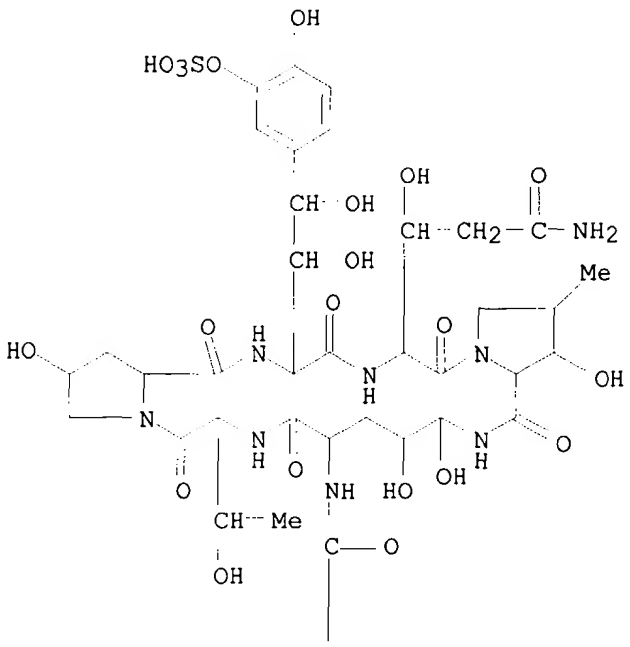
CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-

hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]-, monosodium salt (9CI) (CA INDEX NAME)

PAGE 1-A



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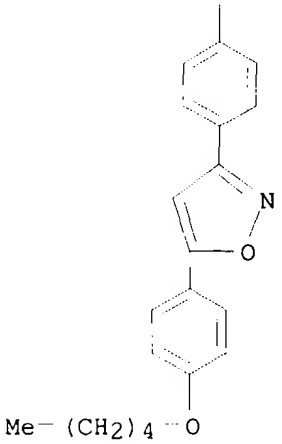

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REFERENCE COUNT: 45 THERE ARE 45 CITED REFERENCES AVAILABLE

Searcher : Shears 308-4994

FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

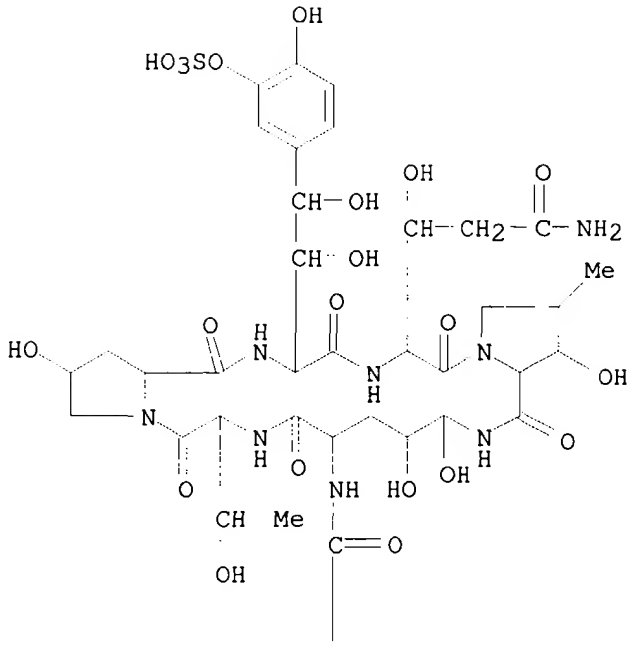
L13 ANSWER 25 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:367628 HCAPLUS
DOCUMENT NUMBER: 133:99146
TITLE: Efficacy of FK463, a (1,3)-β-D-glucan synthase inhibitor, in disseminated azole-resistant Candida albicans infection in mice
AUTHOR(S): Maesaki, Shigefumi; Hossain, Mohammad Ashraf; Miyazaki, Yoshitsugu; Tomono, Kazunori; Tashiro, Takayoshi; Kohno, Shigeru
CORPORATE SOURCE: The Second Department of Internal Medicine, Nagasaki University School of Medicine, Nagasaki, 852-8501, Japan
SOURCE: Antimicrobial Agents and Chemotherapy (2000), 44(6), 1728-1730
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The efficacy of FK463, a new (1,3)-β-D-glucan synthase inhibitor, against azole-resistant Candida albicans strains has been studied. The MIC of FK463 was lower than those of azoles and **amphotericin B** against CDR1-expressing C26 and CaMDR-expressing C40 strains. All mice treated with FK463 (1 mg/kg) survived disseminated murine candidiasis. The fungal burden in the kidney after 6 days was markedly reduced after therapy with FK463 and **amphotericin B** sodium deoxycholate, and plasma (1,3)-β-D-glucan concentration was found to be lower in FK463-treated mice. In our study, FK463 was found to be a potent antifungal agent against disseminated infection with azole-resistant C. albicans.

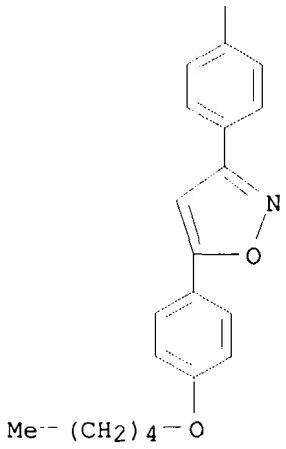
IT **208538-73-2**, FK463
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(efficacy of FK463 in disseminated azole-resistant Candida albicans infection)

RN 208538-73-2 HCAPLUS
CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]-, monosodium salt (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



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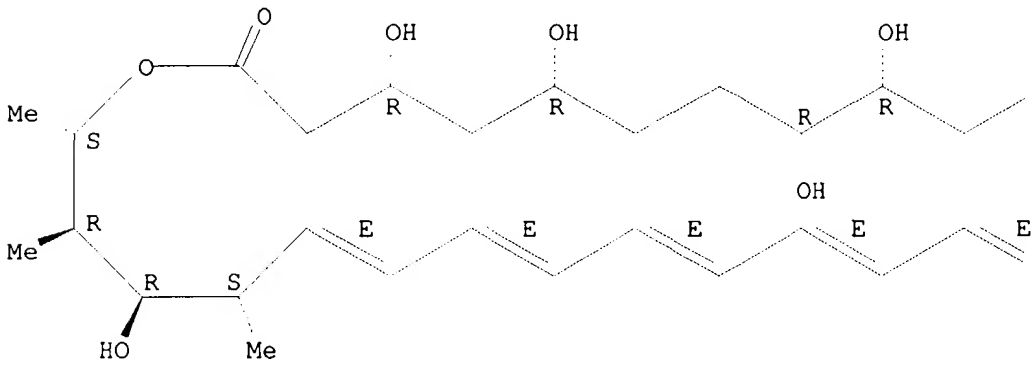
IT **1397-89-3, Amphotericin B**
65277-42-1, Ketoconazole 84625-61-6,
Itraconazole 86386-73-4, Fluconazole
RL: BAC (Biological activity or effector, except adverse); BSU

(Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(efficacy of FK463 in disseminated azole-resistant Candida albicans infection: comparison with other antifungals)

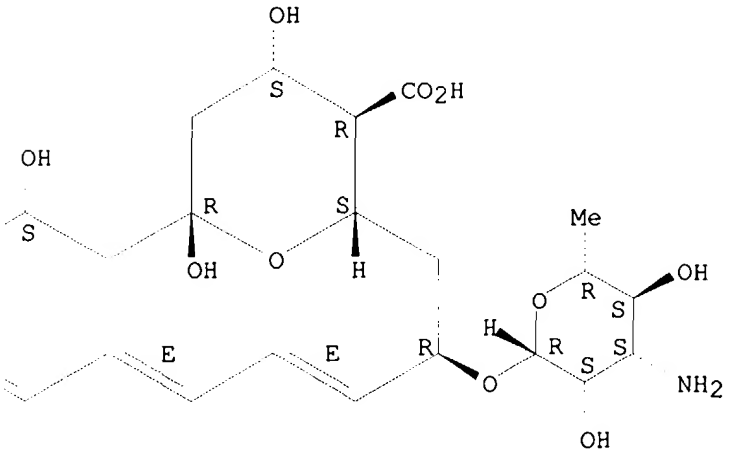
RN 1397-89-3 HCAPLUS
CN Amphotericin B (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A

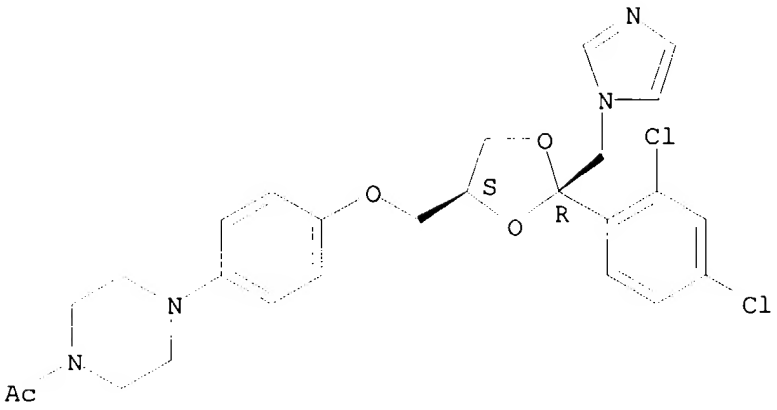


PAGE 1-B



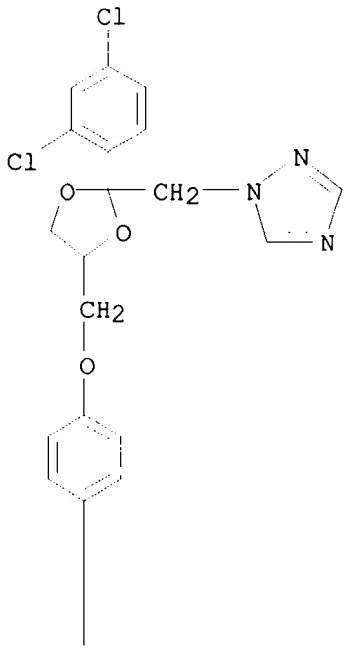
RN 65277-42-1 HCAPLUS
CN Piperazine, 1-acetyl-4-[4-[[(2R,4S)-2-(2,4-dichlorophenyl)-2-(1H-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-, rel- (9CI) (CA INDEX NAME)

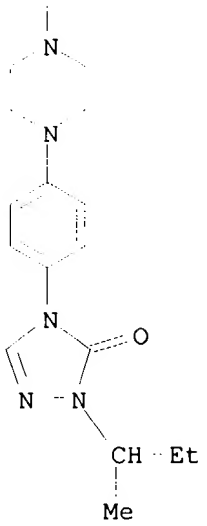
Relative stereochemistry.



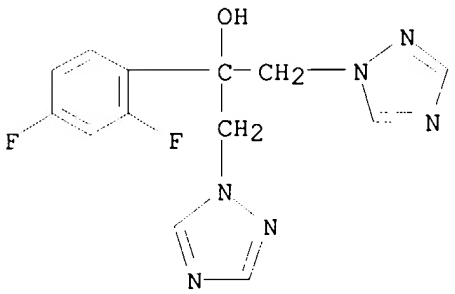
RN 84625-61-6 HCAPLUS
CN 3H-1,2,4-Triazol-3-one, 4-[4-[4-[4-[[2-(2,4-dichlorophenyl)-2-(1H-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)- (9CI) (CA INDEX NAME)

PAGE 1-A





RN 86386-73-4 HCAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 26 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:145288 HCAPLUS
DOCUMENT NUMBER: 132:273894
TITLE: Efficacy of FK463, a new lipopeptide antifungal agent, in mouse models of pulmonary aspergillosis
AUTHOR(S): Matsumoto, Satoru; Wakai, Yoshimi; Nakai, Toru; Hatano, Kazuo; Ushitani, Tomoe; Ikeda, Fumiaki; Tawara, Shuichi; Goto, Toshio; Matsumoto, Fumio; Kuwahara, Shogo
CORPORATE SOURCE: Medicinal Biology Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., Osaka, 532-8514, Japan
SOURCE: Antimicrobial Agents and Chemotherapy (2000),

44(3), 619-621
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

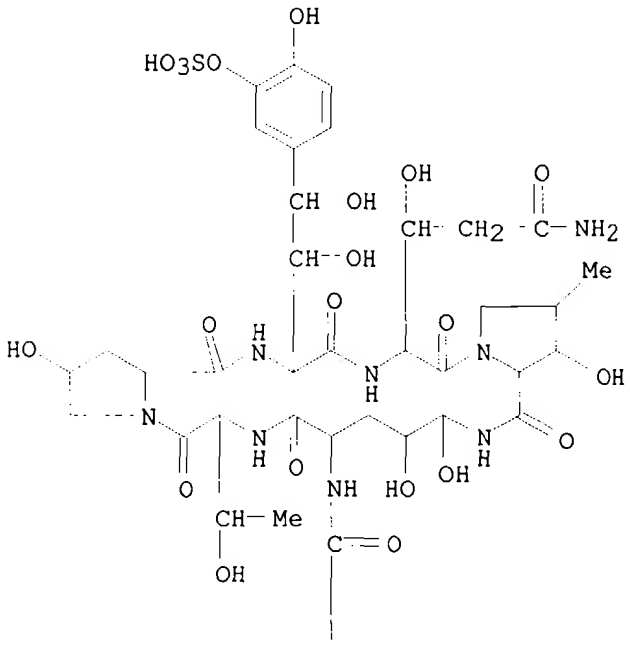
AB The efficacy of FK463, a novel water-soluble lipopeptide, was evaluated in mouse models of pulmonary aspergillosis and was compared with that of **amphotericin B** (AMPH-B). In the pulmonary aspergillosis models induced by intranasal inoculation, FK463 exhibited good efficacy, with 50% EDs in the range of 0.26 to 0.51 mg/kg of body weight; these values were comparable to those of AMPH-B. In an Aspergillus target organ assay with immunosuppressed mice, under conditions of constant plasma levels of FK463, using a s.c. implanted osmotic pressure pump, a significant reduction in viable fungal cells was observed at plasma FK463 levels of 0.55 to 0.80 μg/mL or higher. We conclude that FK463 is highly effective in the treatment of pulmonary aspergillosis in this animal model. These results indicate that FK463 may be a potent parenterally administered antifungal agent for pulmonary aspergillosis.

IT **208538-73-2**, FK463
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(efficacy of FK463 in models of pulmonary aspergillosis)

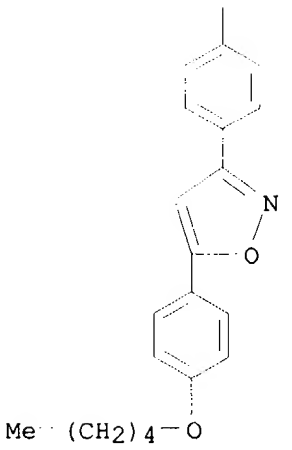
RN 208538-73-2 HCAPLUS

CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]-, monosodium salt (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



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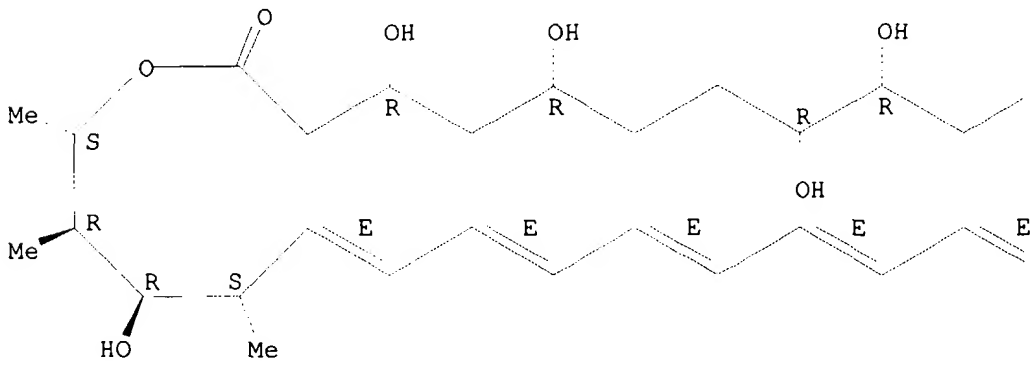
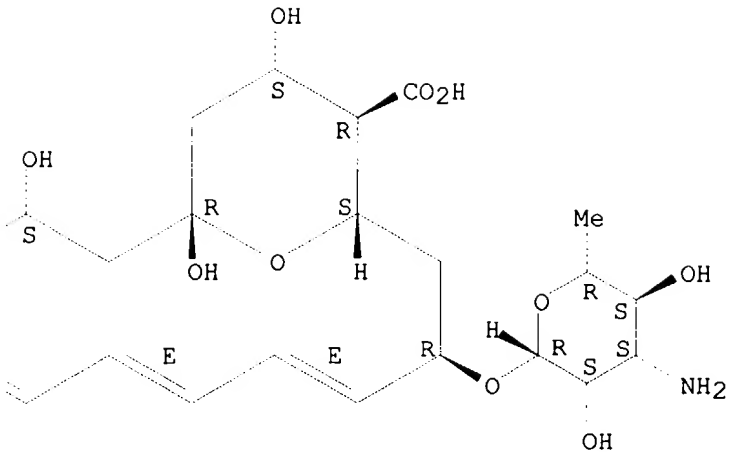
IT **1397-89-3, Amphotericin B**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(efficacy of FK463 in models of pulmonary aspergillosis: comparison with **amphotericin B**)
RN 1397-89-3 HCAPLUS
CN Amphotericin B (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

PAGE 1-A





REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 27 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:145287 HCAPLUS
DOCUMENT NUMBER: 132:273893
TITLE: Efficacy of FK463, a new lipopeptide antifungal agent, in mouse models of disseminated candidiasis and aspergillosis
AUTHOR(S): Ikeda, Fumiaki; Wakai, Yoshimi; Matsumoto, Satoru; Maki, Katsuyuki; Watabe, Etsuko; Tawara, Shuichi; Goto, Toshio; Watanabe, Yuji; Matsumoto, Fumio; Kuwahara, Shogo
CORPORATE SOURCE: Medicinal Biology Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., Osaka, 532-8514, Japan
SOURCE: Antimicrobial Agents and Chemotherapy (2000), 44(3), 614-618
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The efficacy of i.v. injection of FK463, a novel water-soluble lipopeptide, was evaluated in mouse models of disseminated candidiasis and aspergillosis and was compared with those of **fluconazole** (FLCZ) and **amphotericin B** (AMPH-B). In the candidiasis model, FK463 significantly prolonged the survival of i.v. infected mice at doses of 0.125 mg/kg of body weight or higher. In disseminated candidiasis caused by Candida species, including FLCZ-resistant Candida albicans, FK463 exhibited an efficacy 1.4 to 18 times inferior to that of AMPH-B, with 50% EDs (ED50s) ranging from 0.21 to 1.00 mg/kg and 0.06 to 0.26 mg/kg, resp., and was much more active than FLCZ. The protective effect of

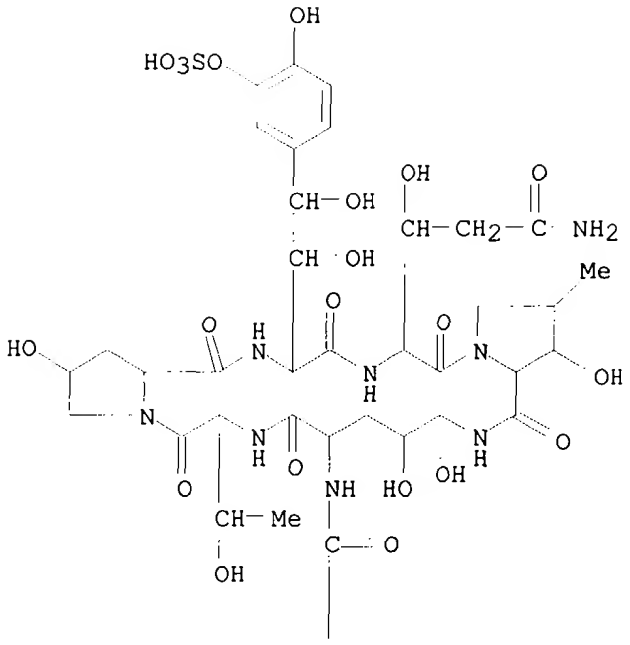
FK463 was not obviously influenced by the fungal inoculum size, the starting time of the treatment, or the immunosuppressed status of the host. The reduction in efficacy was less than that observed with FLCZ or AMPH-B. The efficacy of FK463 was also evaluated in the disseminated candidiasis target organ assay and was compared with those of FLCZ and AMPH-B. Efficacies were evaluated on the basis of a comparison between the mean log10 CFU in kidneys in the groups treated with antifungal agents and that in control group. A single dose of FK463 at 0.5 mg/kg or higher significantly reduced the viable counts in kidneys compared with the nos. of yeast cells before treatment, and its efficacy was comparable to that of AMPH-B, while FLCZ at 4 mg/kg showed only a suppressive effect on the growth of C. albicans in the kidneys. In the disseminated aspergillosis model, FK463 given at doses of 0.5 mg/kg or higher significantly prolonged the survival of mice infected i.v. with Aspergillus fumigatus conidia. The efficacy of FK463 was about 2 times inferior to that of AMPH-B, with ED50s ranging from 0.25 to 0.50 mg/kg and 0.11 to 0.29 mg/kg, resp. These results indicate that FK463 may be a potent parenterally administered therapeutic agent for disseminated candidiasis and aspergillosis.

IT **208538-73-2**, FK463
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(efficacy of FK463 in models of disseminated candidiasis and aspergillosis)

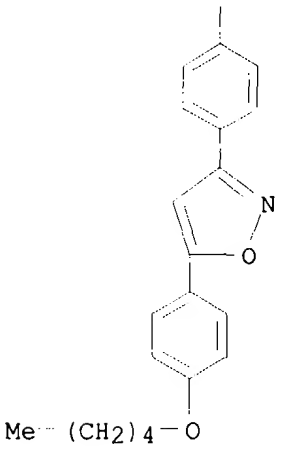
RN 208538-73-2 HCAPLUS

CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]-, monosodium salt (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A



Na

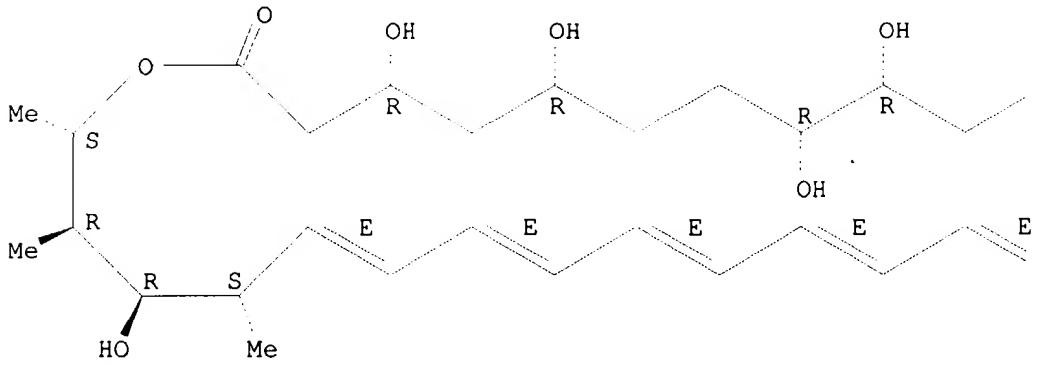
IT **1397-89-3, Amphotericin B**
86386-73-4, Fluconazole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL

(Biological study); USES (Uses)
(efficacy of FK463 in models of disseminated candidiasis and aspergillosis: comparison with **fluconazole** and **amphotericin B**)

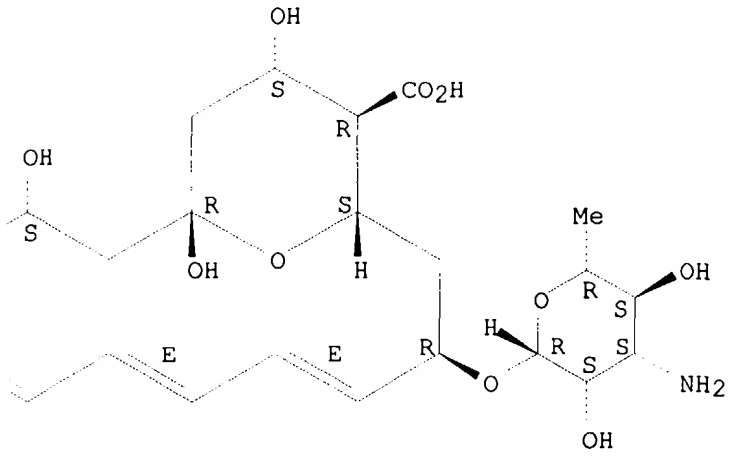
RN 1397-89-3 HCAPLUS
CN Amphotericin B (8CI, 9CI) (CA INDEX NAME)

Absolute stereochemistry.
Double bond geometry as shown.

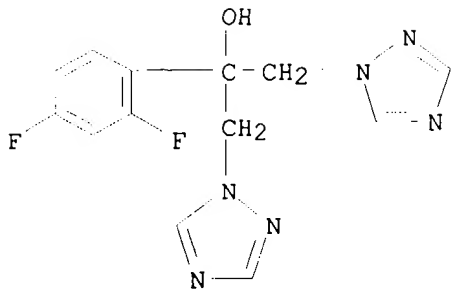
PAGE 1-A



PAGE 1-B



RN 86386-73-4 HCAPLUS
CN 1H-1,2,4-Triazole-1-ethanol, α-(2,4-difluorophenyl)-α-(1H-1,2,4-triazol-1-ylmethyl)- (9CI) (CA INDEX NAME)



REFERENCE COUNT: 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 28 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:11442 HCAPLUS
DOCUMENT NUMBER: 132:148942
TITLE: In vitro activities of a new lipopeptide antifungal agent, FK463, against a variety of clinically important fungi
AUTHOR(S): Tawara, Shuichi; Ikeda, Fumiaki; Maki, Katsuyuki; Morishita, Yoshihiko; Otomo, Kazumi; Teratani, Noriko; Goto, Toshio; Tomishima, Masaki; Ohki, Hidenori; Yamada, Akira; Kawabata, Koji; Takasugi, Hisashi; Sakane, Kazuo; Tanaka, Hirokazu; Matsumoto, Fumio; Kuwahara, Shogo
CORPORATE SOURCE: Medicinal Biology Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., Osaka, 532-8514, Japan
SOURCE: Antimicrobial Agents and Chemotherapy (2000), 44(1), 57-62
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The in vitro antifungal activity and spectrum of FK463 were compared with those of **amphotericin B**, **fluconazole**, and **itraconazole** by using a broth microdilution method specified by National Committee for Clin. Laboratory Stds. document M27-A (National Committee for Clin. Laboratory Stds., Wayne, Pa., 1997). FK463 exhibited broad-spectrum activity against clin. important pathogens including Candida species (MIC range, 0.0039 to 2 μg/mL) and Aspergillus species (MIC range, 0.0039 to 0.0313 μg/mL), and its MICs for such fungi were lower than those of the other antifungal agents tested. FK463 was also potently active against azole-resistant Candida albicans as well as azole-susceptible strains, and there was no cross-resistance with azoles. FK463 showed fungicidal activity against C. albicans, i.e., a 99% reduction in viability after a 24-h exposure at concns. above 0.0156 μg/mL. The min. fungicidal concentration (MFC) assays indicated that FK463 was fungicidal against most isolates of Candida species. In contrast, the MFCs of FK463 for A. fumigatus isolates were much higher than the MICs, indicating that its action is fungistatic against this species. FK463 had no activity against Cryptococcus neoformans, Trichosporon species, or Fusarium solani. Neither the

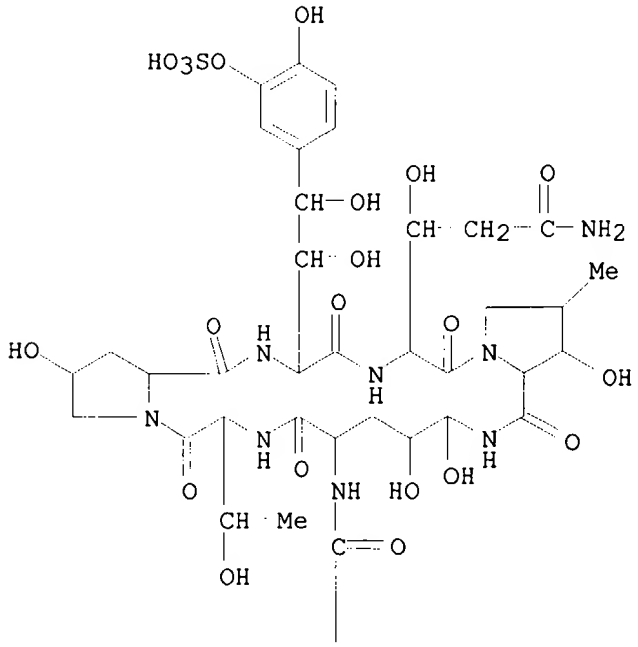
test medium (kind and pH) nor the inoculum size greatly affected the MICs of FK463, while the addition of 4% human serum albumin increased the MICs for Candida species and A. fumigatus more than 32 times. Results from preclin. in vitro evaluations performed thus far indicate that FK463 should be a potent parenteral antifungal agent.

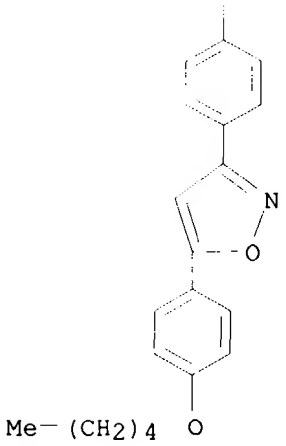
IT **208538-73-2**, FK463
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(in vitro activities of the new lipopeptide antifungal agent FK463 against a variety of clin. important fungi)

RN 208538-73-2 HCAPLUS

CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]-, monosodium salt (9CI) (CA INDEX NAME)

PAGE 1-A





REFERENCE COUNT: 19 THERE ARE 19 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 29 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:150173 HCAPLUS
DOCUMENT NUMBER: 131:13178
TITLE: FK-463: Antifungal
AUTHOR(S): Fromtling, Robert A.; Castaner, J.
CORPORATE SOURCE: Liaison-International, Merck Research Laboratories, Rahway, NJ, 07065-0900, USA
SOURCE: Drugs of the Future (1998), 23(12), 1273-1278
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with 26 refs. FK-463 represents the latest lead in a novel chemical class of echinocandin-like lipopeptide antifungal compds. This agent has potent in vitro and exptl. in vivo activity against a variety of pathogenic Candida species (yeasts) and A. fumigatus (filamentous fungus). This compound has favorable exptl. pharmacokinetics and a unique mode of action which makes it active against fungal isolates that are resistant to established antifungal agents particularly the triazole agent **fluconazole**. This new lead compound is undergoing extensive preclin. evaluation in Japan to determine whether it may be a candidate for further development as a novel antifungal agent. Single-dose and initial multiple-dose phase I studies in normal human volunteers have been completed with the compound being generally well tolerated. FK-463 has advanced to phase II clin. trials (26).

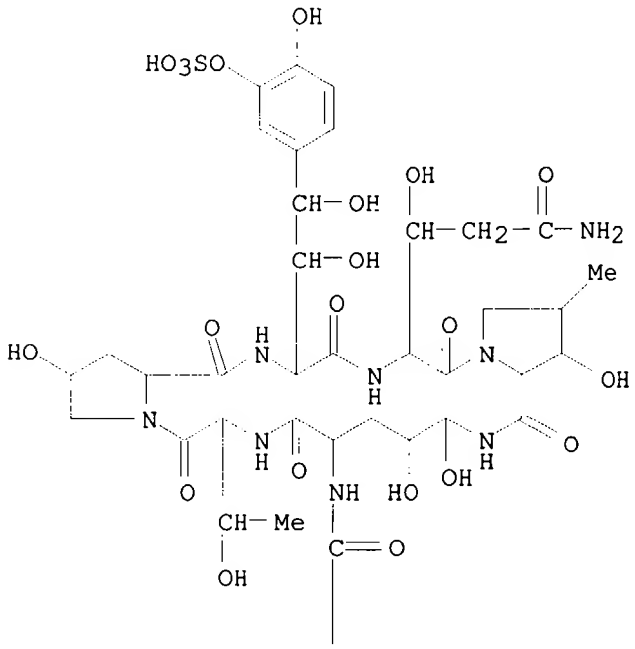
IT **208538-73-2**, FK 463
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES

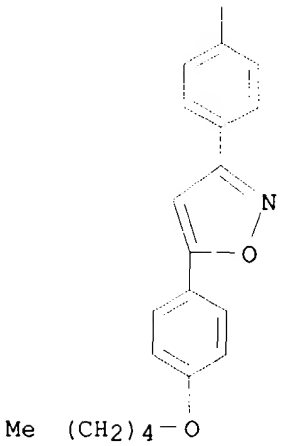
(Uses)
(FK-463 as echinocandin-like lipopeptide antifungal compound in humans and laboratory animals)

RN 208538-73-2 HCAPLUS

CN Pneumocandin A0, 1-[(4R,5R)-4,5-dihydroxy-N2-[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]benzoyl]-L-ornithine]-4-[(4S)-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]-L-threonine]-, monosodium salt (9CI) (CA INDEX NAME)

PAGE 1-A





REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L13 ANSWER 30 OF 30 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1995:188505 HCAPLUS
DOCUMENT NUMBER: 122:95899
TITLE: WF11899A, B and C, novel antifungal lipopeptides. II. Biological properties
AUTHOR(S): Iwamoto, Toshiro; Fujie, Akihiko; Nitta, Kumiko; Hashimoto, Seiji; Okuhara, Masakuni; Kohsaka, Masanobu
CORPORATE SOURCE: Exploratory Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., Tsukuba, 300-26, Japan
SOURCE: Journal of Antibiotics (1994), 47(10), 1092-7
CODEN: JANTAJ; ISSN: 0021-8820
PUBLISHER: Japan Antibiotics Research Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB WF11899A, B and C, novel water-soluble lipopeptides related to the echinocandins, possess potent anti-Candida activities. The IC50s of the compds. against four clin. isolates of Candida albicans ranged from 0.004 to 0.03 μg/mL by microbroth dilution assay. These compds. mildly suppressed the growth of Aspergillus fumigatus and A. niger. WF11899A was superior to cilofungin, and equal to **fluconazole**. 1,3-β-Glucan synthase was inhibited by these compds. at the IC50s of 0.7, 0.7 and 1.8 μg/mL for WF11899A, B and C, resp. However, they hemolyzed mouse red blood cells in vitro at the concentration of 62 μg/mL.

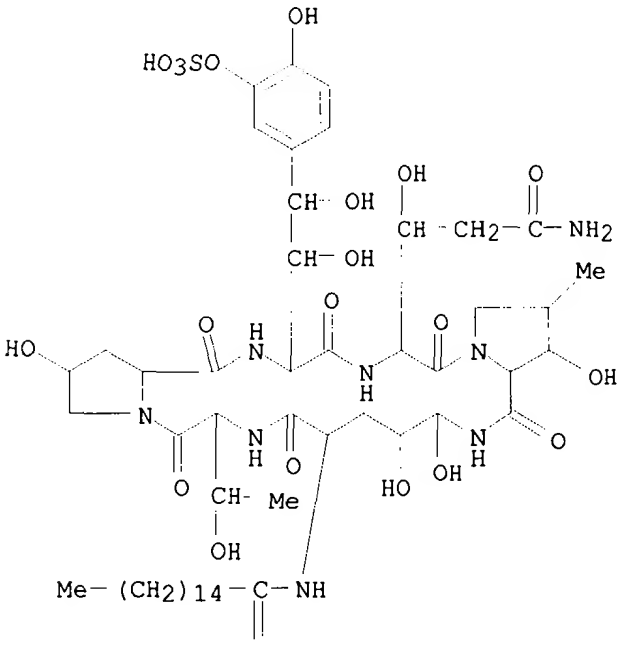
IT **160335-87-5**, WF 11899A **160335-88-6**, WF 11899B
160335-89-7, WF 11899C
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(WF11899A, B and C antifungal activity)

RN 160335-87-5 HCAPLUS

CN Proline, 4,5-dihydroxy-N2-(1-oxohexadecyl)ornithylthreonyl-4-hydroxyprolyl-4-hydroxy-4-[4-hydroxy-3-(sulfooxy)phenyl]threonyl-3-hydroxyglutaminyl-3-hydroxy-4-methyl-, (6→1)-lactam (9CI) (CA INDEX NAME)

PAGE 1-A

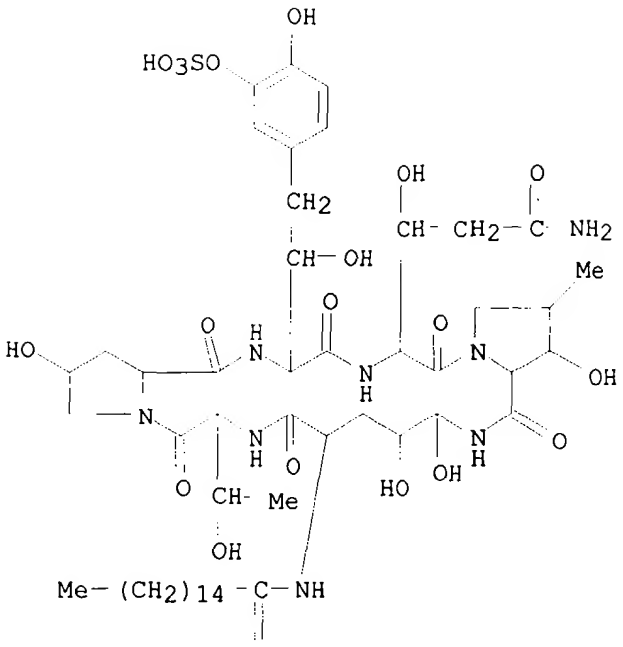


PAGE 2-A

RN 160335-88-6 HCAPLUS

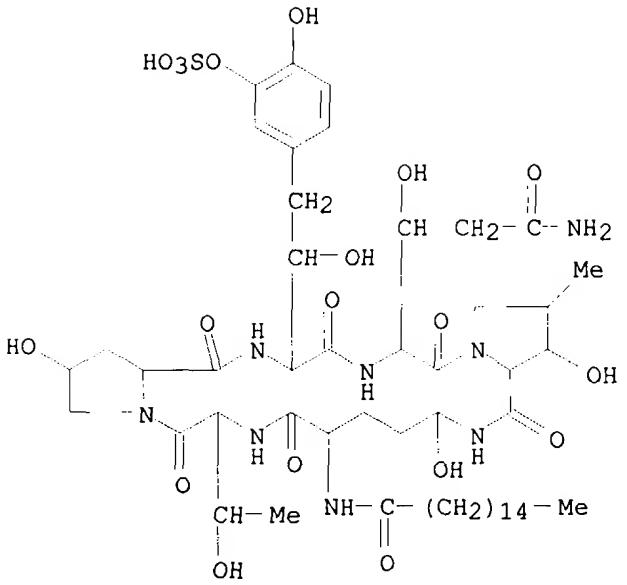
CN Proline, 4,5-dihydroxy-N2-(1-oxohexadecyl)ornithylthreonyl-4-hydroxyprolyl-4-[4-hydroxy-3-(sulfooxy)phenyl]threonyl-3-hydroxyglutaminyl-3-hydroxy-4-methyl-, (6→1)-lactam (9CI) (CA INDEX NAME)

PAGE 1-A



PAGE 2-A

RN 160335-89-7 HCAPLUS
CN Proline, 5-hydroxy-N2-(1-oxohexadecyl)ornithylthreonyl-4-hydroxyprolyl-4-[4-hydroxy-3-(sulfooxy)phenyl]threonyl-3-hydroxyglutaminyl-3-hydroxy-4-methyl-, (6→1)-lactam (9CI) (CA INDEX NAME)



L14 10 SEA ABB=ON PLU=ON L12 AND (AMPHB OR AMPH B OR FLCZ OR VRC OR AMB OR LAMB OR ITCZ OR KCZ)
L15 0 SEA ABB=ON PLU=ON L14 NOT L13

(FILE 'REGISTRY' ENTERED AT 15:01:18 ON 22 OCT 2003)
L16 19 SEA FILE=REGISTRY ABB=ON PLU=ON (1397-89-3/BI OR 235114-32-6/BI OR 86386-73-4/BI OR 208538-73-2/BI OR 84625-61-6/BI OR 137234-62-9/BI OR 65277-42-1/BI OR 171228-49-2/BI OR 2022-85-7/BI OR 1400-61-9/BI OR 182760-06-1/BI OR 22916-47-8/BI OR 11076-17-8/BI OR 160335-87-5/BI OR 160335-88-6/BI OR 160335-89-7/BI OR 312268-90-9/BI OR 539826-01-2/BI OR 72864-26-7/BI)

L17 6 L16 NOT L11 ← Eliminate compds ~~in~~ listed in Claim 4; Restrict to only lipopeptides (Compd I)

(FILE 'CAOLD' ENTERED AT 15:01:58 ON 22 OCT 2003)
L18 0 S L17

FILE 'USPATFULL' ENTERED AT 15:02:04 ON 22 OCT 2003
L19 3 S L17

L19 ANSWER 1 OF 3 USPATFULL on STN
ACCESSION NUMBER: 2002:338190 USPATFULL
TITLE: CYCLOHEXAPEPTIDES HAVING ANTIMICROBIAL ACTIVITY
INVENTOR(S): OHKI, HIDENORI, HYOGO, JAPAN
TOMISHIMA, MASAKI, OSAKA, JAPAN
YAMADA, AKIRA, OSAKA, JAPAN
TAKASUGI, HISASHI, OSAKA, JAPAN

NUMBER	KIND	DATE

Searcher : Shears 308-4994

PATENT INFORMATION:	US 2002193560	A1	20021219
APPLICATION INFO.:	US 1999-308237	A1	19990521 (9)
	WO 1997-JP4193		19971118

	NUMBER	DATE
PRIORITY INFORMATION:	AU 1996-3814	19961125

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: OBLON SPIVAK MCCLELLAND, MAIER & NEUSTADT, 1755 JEFFERSON DAVIS HIGHWAY, FOURTH FLOOR, ARLINGTON, VA, 22202
NUMBER OF CLAIMS: 14
EXEMPLARY CLAIM: 1
LINE COUNT: 2646
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to new polypeptide compounds represented by general formula (I), wherein R 1 and R 2 are as defined in the description and pharmaceutically acceptable salt thereof which have antimicrobial activities (especially antifungal activities), inhibitory activity on &bgr; -1,3-glucan synthase, to process for preparation thereof, to a pharmaceutical composition comprising the same, and to a method for the prophylactic and/or therapeutic treatment of infectious disease including Pneumocystis carinii infection (e.g. Pneumocystis carinii pneumonia in a human being or an animal.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L19 ANSWER 2 OF 3 USPATFULL on STN
ACCESSION NUMBER: 2002:186092 USPATFULL
TITLE: Active agent delivery systems and methods for protecting and administering active agents
INVENTOR(S): Piccariello, Thomas, Blacksburg, VA, UNITED STATES
Olon, Lawrence P., Bristol, TN, UNITED STATES
Kirk, Randal J., Radford, VA, UNITED STATES

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002099013	A1	20020725
APPLICATION INFO.:	US 2001-933708	A1	20010822 (9)

	NUMBER	DATE
PRIORITY INFORMATION:	US 2001-274622P	20010308 (60)
	US 2000-247621P	20001114 (60)
	US 2000-247620P	20001114 (60)
	US 2000-247595P	20001114 (60)
	US 2000-247594P	20001114 (60)
	US 2000-247635P	20001114 (60)
	US 2000-247634P	20001114 (60)
	US 2000-247606P	20001114 (60)
	US 2000-247607P	20001114 (60)
	US 2000-247608P	20001114 (60)
	US 2000-247609P	20001114 (60)
	US 2000-247610P	20001114 (60)
	US 2000-247611P	20001114 (60)

US 2000-247702P	20001114 (60)
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US 2000-247832P	20001114 (60)
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US 2000-247632P	20001114 (60)
US 2000-247631P	20001114 (60)
US 2000-247630P	20001114 (60)

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: Robert M. Schulman, Esq., Hunton & Williams, Suite 1200, 1900 K Street, N.W., Washington, DC, 20006-1100
NUMBER OF CLAIMS: 40
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 8 Drawing Page(s)
LINE COUNT: 2048
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB A composition comprising a polypeptide and an active agent covalently attached to the polypeptide. Also provided is a method for delivery of an active agent to a patient comprising administering to the patient a composition comprising a polypeptide and an active agent covalently attached to the polypeptide. Also provided is a method for protecting an active agent from degradation comprising covalently attaching the active agent to a polypeptide. Also provided is a method for controlling release of an active agent from a composition comprising covalently attaching the active agent to the polypeptide.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L19 ANSWER 3 OF 3 USPATFULL on STN

ACCESSION NUMBER:	2001:199724 USPATFULL			
TITLE:	Intranasal cyclic peptide formulations			
INVENTOR(S):	Horii, Ikuo, Yokohama-shi, Japan Kobayashi, Kazuko, Kamakura-shi, Japan Shimma, Nobuo, Chigasaki-shi, Japan Yanagawa, Akira, Yokohama-shi, Japan			
	NUMBER	KIND	DATE	
PATENT INFORMATION:	US 2001038824	A1	20011108	
APPLICATION INFO.:	US 2001-765846	A1	20010119	(9)
	NUMBER		DATE	
PRIORITY INFORMATION:	ET 2000-101057		20000120	
DOCUMENT TYPE:	Utility			
FILE SEGMENT:	APPLICATION			
LEGAL REPRESENTATIVE:	George W. Johnston, Hoffmann-La Roche Inc., 340 Kingsland street, Nutley, NJ, 07110			
NUMBER OF CLAIMS:	36			
EXEMPLARY CLAIM:	1			
NUMBER OF DRAWINGS:	11 Drawing Page(s)			
LINE COUNT:	3690			

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

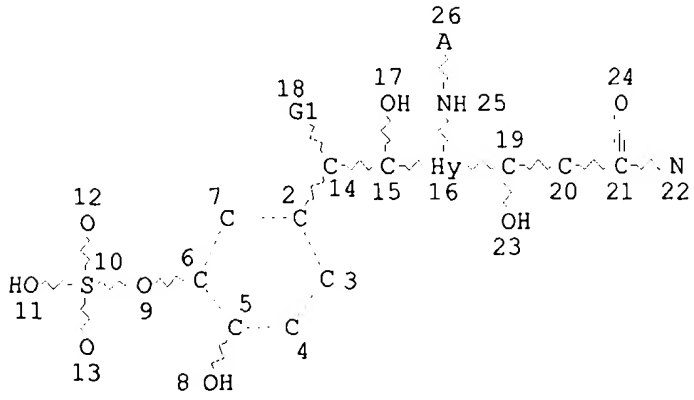
AB The present invention relates to a nasally administrable composition of a physiologically active cyclic peptide and pharmaceutically acceptable salts thereof that is prepared by homogeneously dispersing a physiologically active cyclic peptide such as antifungal cyclic peptides (aerothricins, echinocandin analogs, pneumocandin analogs, and aureobacidines), antibacterial cyclic peptides (e.g. vancomycin, daptomycin), cyclosporin A, lanreotide, vapreotide, vasopressin antagonist (U.S. Pat. Number 5,095,003) and eptifibatide in unique carrier, i.e. a physiologically acceptable powdery or crystalline carrier containing a water insoluble polyvalent metal carrier, or organic carrier having a mean particle size of 20 to 500 μm, in the presence or absence of an absorption enhancer and by homogeneously adsorbing onto the carrier, and its use for therapeutic treatment of disease such as systemic fungal infections by intranasal administration.

The composition can be nasally administered in powder form.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

(FILE 'MARPAT' ENTERED AT 15:12:36 ON 22 OCT 2003)

L31 STR



VAR G1=H/OH
NODE ATTRIBUTES:
NSPEC IS RC AT 26
CONNECT IS X2 RC AT 3
CONNECT IS X2 RC AT 4
CONNECT IS X2 RC AT 7
DEFAULT MLEVEL IS ATOM
MLEVEL IS CLASS AT 16
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE

ATTRIBUTES SPECIFIED AT SEARCH-TIME:
ECLEVEL IS LIM ON ALL NODES
ALL RING(S) ARE ISOLATED

L33 27 SEA FILE=MARPAT SSS FUL L31 (MODIFIED ATTRIBUTES)

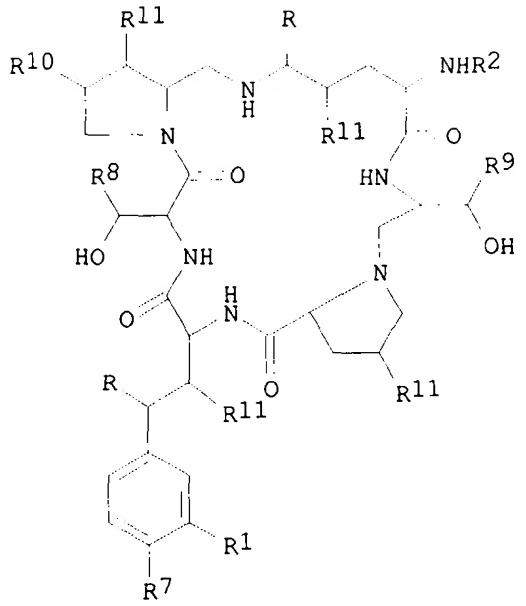
100.0% PROCESSED 2095 ITERATIONS 27 ANSWERS
SEARCH TIME: 00.00.09

L33 ANSWER 1 OF 27 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 136:341005 MARPAT
TITLE: Preparation of cyclic peptide antifungal agents
INVENTOR(S): Burkhardt, Frederick J.; Debono, Manuel; Nissen, Jeffrey S.; Turner, William W., Jr.
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: U.S., 33 pp., Cont.-in-part of U.S. 5,965,525. CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE

US 6384013	B1	20020507	US 1999-291900	19990414
ZA 9301830	A	19940915	ZA 1993-1830	19930315
IL 122315	A1	20020310	IL 1993-122315	19930315
JP 2002226500	A2	20020814	JP 2002-3969	19930318
US 5965525	A	19991012	US 1995-449056	19950524
US 5932543	A	19990803	US 1997-873480	19970612
PRIORITY APPLN. INFO.:			US 1992-854117	19920319
			US 1992-992390	19921216
			US 1993-32228	19930317
			US 1995-449056	19950524
			IL 1993-105048	19930315
			JP 1993-58529	19930318

GI



I

AB Acyl cyclic peptides I (R, R11 = H, OH; R1 = H, OH, OSO3H; R2 = an acyl side chain; R7 = R1, phosphonooxy; R8 = H, Me, H2NCOCH2; R9, R10 = Me, H) were prepared as fungicides. Thus, I [R = R11 = OH, R1 = H, R2 = p-(pentyoxy)-p-terphenyl, R8 = R9 = R10 = Me, R7 = phosphonooxy] was prepared in chiral form (echinocandin B derivative) by N-acylation and selective O-phosphonylation. Compds. I are especially active against the infectious fungi Candida albicans and Candida parasilosis and inhibit the growth of Pneumocystis carinii, the causative organism of pneumocystis pneumonia in AIDs sufferers.

IC ICM A61K038-00
NCL 514011000
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1
ST peptide cyclic prepn fungicide; echinocandin analog prepn fungicide
IT Peptides, preparation
RL: BSU (Biological study, unclassified); SPN (Synthetic

preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclic; preparation of cyclic peptides as fungicides)

IT Fungicides
(preparation of cyclic peptides as fungicides)

IT 158935-94-5P 158935-95-6P 158935-96-7P 158935-97-8P
158935-98-9P 158935-99-0P 158936-00-6P 158936-01-7P
158936-02-8P 158936-03-9P 158936-04-0P 158936-05-1P
158936-06-2P 158936-07-3P 158936-08-4P 158936-09-5P
158936-10-8P 158936-11-9P 158936-12-0P 158936-13-1P
158936-14-2P 158936-15-3P 158936-16-4P 158936-17-5P
158936-18-6P 158936-19-7P 158936-20-0P 158936-21-1P
158936-22-2P 158936-23-3P 158936-24-4P 158936-25-5P
158936-26-6P 158936-27-7P 158936-28-8P 158936-29-9P
158936-30-2P 158936-31-3P 158936-32-4P 158936-33-5P
158936-34-6P 158936-35-7P 158936-36-8P 158936-37-9P
158936-38-0P 158936-39-1P 158936-40-4P 158936-41-5P
158936-42-6P 158936-43-7P 158936-44-8P 158936-45-9P
158936-46-0P 158936-47-1P 158936-48-2P 158936-49-3P
158936-50-6P 158936-51-7P 158936-52-8P 158936-53-9P
158936-54-0P 158936-55-1P 158936-56-2P 158936-57-3P
158936-58-4P 158936-59-5P 158936-60-8P 158936-61-9P
158936-62-0P 158936-63-1P 158936-64-2P 158936-65-3P
158936-66-4P 158936-67-5P 158936-68-6P 158936-69-7P
158936-70-0P 158936-71-1P 158936-72-2P 158936-73-3P
158936-74-4P 158936-75-5P 158936-76-6P 158936-77-7P
158936-78-8P 158936-79-9P 158936-80-2P 158936-81-3P
158936-82-4P 158936-83-5P 158936-84-6P 158936-85-7P
158936-86-8P 158936-87-9P 158936-88-0P 158936-89-1P
158936-90-4P 158936-91-5P 159000-67-6P 166663-26-9P
166663-28-1P 183211-59-8P 183211-60-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of cyclic peptides as fungicides)

IT 107-08-4, 1-Iodopropane 107-82-4 110-53-2, 1-Bromopentane
111-66-0, 1-Octene 536-74-3 540-38-5, 4-Iodophenol 542-69-8,
1-Iodobutane 619-44-3, Methyl 4-iodobenzoate 629-05-0, 1-Octyne
638-45-9, 1-Iodohexane 693-02-7, 1-Hexyne 764-93-2, 1-Decyne
1066-54-2 1647-26-3, 1-Bromo-2-cyclohexylethane 2038-91-7
2346-07-8 2527-99-3, Methyl 5-bromofuran-2-carboxylate
2916-68-9, 2-(Trimethylsilyl)ethanol 3034-86-4 6661-54-7
13295-53-9, Cyclobutylmethyl tosylate 21856-53-1,
Cyclopentylmethyl tosylate 29558-77-8 60834-63-1 62124-28-1
63619-51-2 63619-63-6 63619-64-7 79404-91-4, Cilofungin
79411-15-7 108366-80-9 141430-54-8 158407-15-9 158937-74-7
158937-75-8 158937-76-9 158937-77-0 158937-78-1 158937-79-2
158937-80-5 158937-81-6 158937-82-7 158937-83-8 158937-84-9
158937-85-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of cyclic peptides as fungicides)

IT 166663-25-8P 213669-65-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of cyclic peptides as fungicides)

IT 5731-15-7P 25739-23-5P 41424-11-7P 42497-80-3P 52364-71-3P
52709-87-2P 59748-14-0P 59748-15-1P 59748-16-2P 75867-41-3P
82175-72-2P 89752-76-1P 117802-43-4P 117802-44-5P

118788-02-6P 140714-91-6P 144493-15-2P 144540-61-4P
158936-92-6P 158936-93-7P 158936-94-8P 158936-95-9P
158936-96-0P 158936-97-1P 158936-98-2P 158936-99-3P
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158937-04-3P 158937-05-4P 158937-06-5P 158937-07-6P
158937-08-7P 158937-09-8P 158937-10-1P 158937-11-2P
158937-12-3P 158937-13-4P 158937-14-5P 158937-15-6P
158937-16-7P 158937-17-8P 158937-18-9P 158937-19-0P
158937-20-3P 158937-21-4P 158937-22-5P 158937-23-6P
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158937-32-7P 158937-33-8P 158937-34-9P 158937-35-0P
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158937-56-5P 158937-57-6P 158937-58-7P 158937-59-8P
158937-60-1P 158937-61-2P 158937-62-3P 158937-63-4P
158937-64-5P 158937-65-6P 158937-66-7P 158937-67-8P
158937-68-9P 158937-69-0P 158937-70-3P 158937-71-4P
158937-72-5P 158937-73-6P 158937-86-1P 158937-87-2P
158937-88-3P 158937-89-4P 158937-90-7P 158937-91-8P
158937-92-9P 158937-93-0P 158937-94-1P 158937-95-2P
158937-96-3P 158937-97-4P 158937-98-5P 158937-99-6P
158938-00-2P 158938-01-3P 158938-02-4P 158938-03-5P
158938-04-6P 158938-05-7P 158938-06-8P 158938-07-9P
158938-08-0P 158938-09-1P 158938-10-4P 158938-11-5P
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158938-16-0P 158938-17-1P 160442-19-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of cyclic peptides as fungicides)

REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 2 OF 27 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 136:194225 MARPAT
TITLE: Antifungal combination use of granulocyte-colony stimulating factor and lipopeptide compound
INVENTOR(S): Ikeda, Fumiaki; Watabe, Etsuko; Matsumoto, Satoru; Ushitani, Tomoe; Koide, Yasuto
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002013846	A2	20020221	WO 2001-JP7009	20010813
WO 2002013846	A3	20030403		
W: JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1317277	A2	20030611	EP 2001-956880	20010813

R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR

PRIORITY APPLN. INFO.: AU 2000-9387 20000814
WO 2001-JP7009 20010813

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB There is described antifungal combination use of granulocyte-colony stimulating factor (GCSF) with a lipopeptide compound I (R1 = acyl; R2, R3 = H, OH) or a salt thereof. The combination of GCSF and II was effective against infection with Candida albicans in mice.

IC ICM A61K038-00

CC 1-5 (Pharmacology)
Section cross-reference(s): 63

ST antifungal granulocyte colony stimulating factor lipopeptide combination; Candida infection GCSF antifungal lipopeptide combination

IT Absidia
Absidia corymbifera
Acremonium
Alternaria
Aspergillus
Aspergillus clavatus
Aspergillus flavus
Aspergillus fumigatus
Aspergillus nidulans
Aspergillus niger
Aspergillus terreus
Aspergillus versicolor
Blastomyces
Blastomyces dermatitidis
Candida
Candida albicans
Candida glabrata
Candida guilliermondii
Candida kefyr
Candida krusei
Candida parapsilosis
Candida tropicalis
Candida utilis
Cladosporium
Cladosporium bantianum
Coccidioides
Coccidioides immitis
Cryptococcus (fungus)
Cryptococcus neoformans
Cunninghamella
Cunninghamella elegans
Curvularia
Drug delivery systems
Epidermophyton
Epidermophyton floccosum
Exophiala
Exophiala dermatitidis

Exophiala spinifera
Fonsecaea
Fonsecaea pedrosoi
Fungicides
Fusarium
Fusarium solani
Geotrichum
Geotrichum candidum
Histoplasma
Histoplasma capsulatum capsulatum
Malassezia
Malassezia furfur
Microsporum
Microsporum canis
Microsporum gypseum
Mucor
Paecilomyces
Paracoccidioides
Paracoccidioides brasiliensis
Penicillium
Penicillium marneffei
Phialophora
Pneumocystis
Pneumocystis carinii
Pseudallescheria
Pseudallescheria boydii
Rhizopus
Rhizopus microsporus rhizopodiformis
Rhizopus oryzae
Saccharomyces
Saccharomyces cerevisiae
Scopulariopsis
Skin-infecting fungi
Sporothrix
Sporothrix schenckii
Trichophyton
Trichophyton mentagrophytes
Trichophyton rubrum
Trichosporon
Trichosporon asahii
Trichosporon cutaneum
Wangiella
(antifungal combination use of granulocyte colony-stimulating factor and lipopeptide compound)

IT Fungi
(dematiaceous; antifungal combination use of granulocyte colony-stimulating factor and lipopeptide compound)

IT Lipopeptides
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibiting cell wall 1,3β-D-glucan synthesis; antifungal combination use of granulocyte colony-stimulating factor and lipopeptide compound)

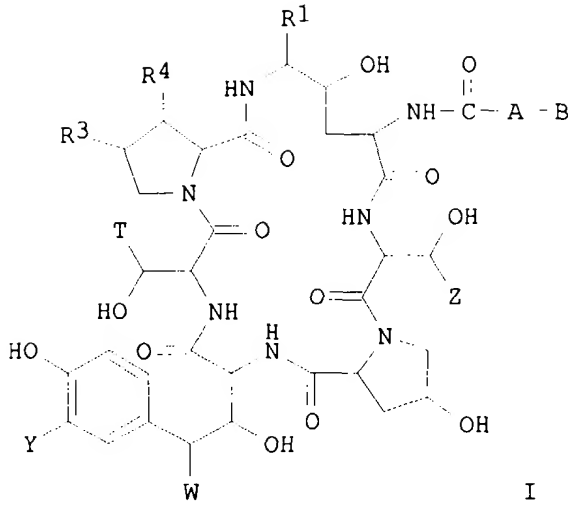
IT 235114-32-6
RL: PAC (Pharmacological activity); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antifungal combination use of granulocyte colony-stimulating factor and lipopeptide compound)

IT 143011-72-7
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antifungal combination use of granulocyte colony-stimulating factor and lipopeptide compound)
IT 9051-97-2
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(cyclic hexapeptide lipopeptide inhibiting cell wall synthesis of; antifungal combination use of granulocyte-colony stimulating factor and lipopeptide compound)

L33 ANSWER 3 OF 27 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 135:180953 MARPAT
TITLE: Preparation of novel echinocandin derivatives as fungicides
INVENTOR(S): Courtin, Olivier; Dussarat, Arlette; Melon-Manguer, Dominique; Schio, Laurent
PATENT ASSIGNEE(S): Aventis Pharma S.A., Fr.
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001060845	A1	20010823	WO 2001-FR419	20010214
W: AE, AG, AL, AU, BA, BB, BG, BR, BZ, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2804957	A1	20010817	FR 2000-1844	20000215
EP 1257568	A1	20021120	EP 2001-907783	20010214
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				
PRIORITY APPLN. INFO.:			FR 2000-1844	20000215
			WO 2001-FR419	20010214

GI



I

AB Echinocandin derivs. I [R1 = H, OH, (un)substituted alkoxy, alkenyloxy or alkynyloxy; R3 = H, Me, OH; R4, W = H, OH; A = O, CH2, NH; B is a steroid residue; T = H, Me, CH2CONH2, CH2C.tplbond.N, (CH2)2NH2 or alkylaminoethyl; Y = H, OH, halo, OSO3H or salts; Z = H, Me] were prepared as antifungal agents. Thus, 1-[(4R,5R)-4,5-dihydroxy-N2-[[[(3β,22E)-ergosta-5,7,22-trien-3-yl]oxy]carbonyl]-L-ornithine]deoxymulundocandin was prepared by treating ergosterol with diphosgene in CH2Cl2 in the presence of Et3N and treating the product with deoxymulundocandin.

IC ICM C07K007-56
ICS A61K038-12; A61P031-10

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 32

ST echinocandin steroid deriv prepn fungicide

IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclic; preparation of novel echinocandin derivs. as fungicides)

IT Fungicides
(preparation of novel echinocandin derivs. as fungicides)

IT 355127-02-5P 355127-03-6P 355127-04-7P 355127-05-8P
355127-06-9P 355127-07-0P 355127-08-1P 355127-09-2P
355127-10-5P 355127-11-6P 355127-12-7P 355127-13-8P
355127-14-9P 355127-15-0P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of novel echinocandin derivs. as fungicides)

IT 57-87-4, Ergosterol 57-88-5, Cholesterol, reactions 79-63-0, Lanosterol 80-97-7, 5α-Cholestan-3β-ol 83-46-5, β-Sitosterol 83-48-7, Stigmasterol 503-38-8, Diphosgene 566-88-1 5927-18-4 108351-20-8, Mulundocandin 138626-63-8, Deoxymulundocandin

RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of novel echinocandin derivs. as fungicides)
IT 24698-89-3P 41238-20-4P 41238-22-6P 154005-59-1P
355127-16-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);
RACT (Reactant or reagent)
(preparation of novel echinocandin derivs. as fungicides)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR *THIS RECORD. ALL CITATIONS AVAILABLE IN* THE RE FORMAT

L33 ANSWER 4 OF 27 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 135:41005 MARPAT
TITLE: Antifungal activity of lipopeptide enhancement by immunosuppressants
INVENTOR(S): Ikeda, Fumiaki; Otomo, Kazumi; Matsumoto, Satoru; Wakai, Yoshimi; Teratani, Noriko
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 30 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001041780	A2	20010614	WO 2000-JP8730	20001208
WO 2001041780	A3	20020510		
W: CA, CN, JP, KR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR				
EP 1239868	A2	20020918	EP 2000-981653	20001208
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI, CY, TR				
JP 2003516359	T2	20030513	JP 2001-543124	20001208
US 2003017975	A1	20030123	US 2002-148876	20020611
PRIORITY APPLN. INFO.:			AU 1999-4623	19991213
			WO 2000-JP8730	20001208

AB The present invention is related to a new use of an immunosuppressant, for increasing the antifungal activity of a lipopeptide compound Thus, a combination of the lipopeptide and an immunosuppressant at certain concns. showed a synergistic effect antifungal efficacy against Aspergillus fumigatus.
IC ICM A61K038-00
CC 1-5 (Pharmacology)
Section cross-reference(s): 63
ST *lipopeptide antifungal immunosuppressant*
IT Drug delivery systems
Fungicides
Immunosuppressants
Packaging materials
(antifungal activity of lipopeptide enhancement by immunosuppressants)
IT Lipopeptides
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)

(antifungal activity of lipopeptide enhancement by immunosuppressants)

IT Drug interactions
(synergistic; antifungal activity of lipopeptide enhancement by immunosuppressants)

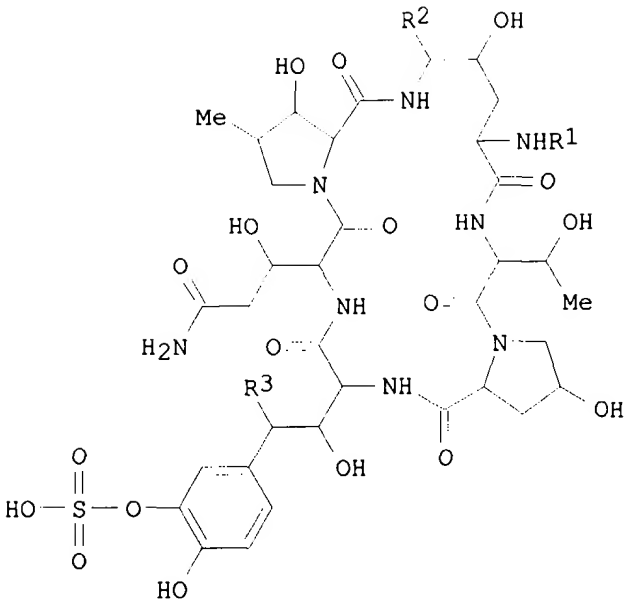
IT 104987-11-3 179165-70-9
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antifungal activity of lipopeptide enhancement by immunosuppressants)

IT 9051-97-2
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(antifungal activity of lipopeptide enhancement by immunosuppressants)

L33 ANSWER 5 OF 27 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 134:27477 MARPAT
TITLE: Antifungal combination use of lipopeptide with other agents
INVENTOR(S): Ikeda, Fumiaki; Otomo, Kazumi; Wakai, Yosimi; Matsumoto, Satoru
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE: PCT Int. Appl., 19 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000072865	A2	20001207	WO 2000-JP3340	20000524
WO 2000072865	A3	20010510		
W: JP, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 1180038	A2	20020220	EP 2000-929859	20000524
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2003527314	T2	20030916	JP 2000-620974	20000524
PRIORITY APPLN. INFO.:			AU 1999-663	19990531
			WO 2000-JP3340	20000524

GI



I

AB There is described antifungal combination use of known antifungal agents such as the azoles or polyenes in combination with a lipopeptide compound antifungal agent. More particularly, the invention relates to antifungal combination use of azoles such as fluconazole, voriconazole, itraconazole, ketoconazole, miconazole, ER 30346 and SCH 56592; polyenes such as amphotericin B, nystatin, liposomal and lipid forms thereof such as Abelcet, AmBisome and Amphocil; purine or pyrimidine nucleotide inhibitors such as flucytosine; or polyoxins such as nikkomycins, in particular nikkomycin Z or nikkomycin X; other chitin inhibitors; elongation factor inhibitors such as sordarin and analogs thereof; mannan inhibitors such as predamycin, bactericidal/permeability-inducing (BPI) protein products such as XMP.97 or XMP.127; or complex carbohydrate antifungal agents such as CAN-296; with a lipopeptide compound (I: R1 = acyl and R2 and R3 = H or OH) as described herein.

IC ICM A61K038-00

CC 10-5 (Microbial, Algal, and Fungal Biochemistry)
Section cross-reference(s): 1, 63

ST antifungal agent lipopeptide combination azole polyene; polyoxin combination lipopeptide antifungal agent

IT Proteins, specific or class
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(BPI (bactericidal/permeability-increasing); antifungal combination use of lipopeptide with other agents such as azoles and polyenes)

IT Alternaria
Aspergillus
Aspergillus fumigatus
Blastomyces
Candida

Candida albicans
Candida neoformans
Coccidioides
Cryptococcus (fungus)
Curvularia
Drug delivery systems
Drug interactions
Exophiala
Fungicides
Fusarium
Histoplasma
Paecilomyces
Paracoccidioides
Penicillium
Pneumocystis carinii
Pseudallescheria
Rhizopus
Saccharomyces
Skin-infecting fungi
Sporothrix
Trichosporon
(antifungal combination use of lipopeptide with other agents such as azoles and polyenes)

IT Lipopeptides
Polyenes
Purine nucleotides
Pyrimidine nucleotides
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antifungal combination use of lipopeptide with other agents such as azoles and polyenes)

IT Fungi
(dematiaceous; antifungal combination use of lipopeptide with other agents such as azoles and polyenes)

IT Elongation factors (protein formation)
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; antifungal combination use of lipopeptide with other agents such as azoles and polyenes)

IT 1397-89-3, Amphotericin B 1400-61-9, Nystatin 2022-85-7, Flucytosine 11076-17-8, Sordarin 11076-17-8D, Sordarin, analogs 22916-47-8, Miconazole 59456-70-1, Nikkomycin Z 65277-42-1, Ketoconazole 72864-26-7, Nikkomycin X 84625-61-6, Itraconazole 86386-73-4, Fluconazole 120895-52-5, Amphocil 137234-62-9, Voriconazole 159862-74-5 168124-75-2 171228-49-2, SCH 56592 182760-06-1, ER 30346 200513-60-6, CAN-296 235114-32-6D, isomers 312268-90-9, Predamycin
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antifungal combination use of lipopeptide with other agents such as azoles and polyenes)

IT 9036-88-8, Mannan
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(inhibitors; antifungal combination use of lipopeptide with other agents such as azoles and polyenes)

L33 ANSWER 6 OF 27 MARPAT COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 134:17732 MARPAT
TITLE: Novel echinocandin derivatives, method for preparing same and use as antifungal agents
INVENTOR(S): Corbier, Alain; Fauveau, Patrick; Pietre-Dischamp, Nathalie; Schio, Laurent; Vicat, Pascale
PATENT ASSIGNEE(S): Hoechst Marion Roussel, Fr.
SOURCE: PCT Int. Appl., 34 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000075178	A1	20001214	WO 2000-FR1569	20000608
W: AE, AG, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2794747	A1	20001215	FR 1999-7252	19990609
EP 1189932	A1	20020327	EP 2000-940456	20000608
EP 1189932	B1	20030521		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2003504309	T2	20030204	JP 2001-502459	20000608
AT 240971	E	20030615	AT 2000-940456	20000608
PRIORITY APPLN. INFO.:			FR 1999-7252	19990609
			WO 2000-FR1569	20000608

OTHER SOURCE(S): CASREACT 134:17732
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention concerns cyclic peptides I wherein: R = chain containing up to 30 carbon atoms, optionally containing one or several heteroatoms, one or several heterocycles; either R1 and R2 = H, OH, alkyl optionally substituted, or NR1 forms with the carbon bearing NR1R2 a double bond and R2 is XRa, X being O, NH or N-alkyl and Ra being H, alkyl optionally substituted; R3 = H, OH, CH3; R4 = H, OH; T = H, CH3, CH2CONH2, CH2CN, (CH2)2NH2; Y = H, OH, halogen, OSO3H; W = H, OH; Z = H or CH3. The products of formula I have antifungal properties. Thus, trans-1-[4-[(2-aminocyclo-hexyl)amino]-N2-[[4-[5-[4-(pentyloxy)phenyl]-3-isoxazolyl]phenyl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B trifluoroacetate was prepared and tested for its inhibition of glucan synthase of Candida albicans.
IC ICM C07K007-56
ICS A61K038-12; A61P031-10
CC 34-3 (Amino Acids, Peptides, and Proteins)

Section cross-reference(s): 1, 10, 63
ST echinocandin cyclic peptide prepn antifungal glucan synthase inhibitor
IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclic; novel echinocandin derivs. method for preparing same and use as glucan synthase inhibitors and antifungal agents)
IT Fungicides
(novel echinocandin derivs. method for preparing same and use as glucan synthase inhibitors and antifungal agents)
IT 9027-19-4, Glucan synthase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Candida albicans; novel echinocandin derivs. method for preparing same and use as glucan synthase inhibitors and antifungal agents)
IT 310459-08-6P 310459-11-1P 310459-20-2P 310459-23-5P
310459-27-9P 310459-30-4P 310459-33-7P 310459-36-0P
310459-39-3P 310459-42-8P 310459-49-5P 310459-52-0P
310459-58-6P 310459-61-1P 310459-67-7P 310459-70-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(novel echinocandin derivs. method for preparing same and use as glucan synthase inhibitors and antifungal agents)
IT 15967-72-3, (S)-Propane-1,2-diamine 20439-47-8 21436-03-3
38734-69-9, Ethylenediamine diacetate 138626-63-8,
Deoxymulundocandin 179165-34-5 310459-15-5 340130-90-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(novel echinocandin derivs. method for preparing same and use as glucan synthase inhibitors and antifungal agents)
IT 227472-53-9P 310459-13-3P 310459-17-7P 310459-44-0P
310459-46-2P 310459-54-2P 340131-54-6P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(novel echinocandin derivs. method for preparing same and use as glucan synthase inhibitors and antifungal agents)
REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 7 OF 27 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 134:17731 MARPAT
TITLE: Echinocandin derivatives, method for preparing same and application as glucan synthase inhibitors and antifungal agents
INVENTOR(S): Fauveau, Patrick; Hawser, Stephen; Lebourg, Gilles; Schio, Laurent
PATENT ASSIGNEE(S): Hoechst Marion Roussel, Fr.
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000075177	A1	20001214	WO 2000-FR1568	20000608
W: AE, AG, AL, AU, BA, BB, BG, BR, CA, CN, CR, CU, CZ, DM, DZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MA, MG, MK, MN, MX, MZ, NO, NZ, PL, RO, SG, SI, SK, TR, TT, UA, US, UZ, VN, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2794746	A1	20001215	FR 1999-7251	19990609
FR 2794746	B1	20021206		
EP 1189933	A1	20020327	EP 2000-942169	20000608
EP 1189933	B1	20030409		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2003501441	T2	20030114	JP 2001-502458	20000608
AT 236928	E	20030415	AT 2000-942169	20000608
PRIORITY APPLN. INFO.:			FR 1999-7251	19990609
			WO 2000-FR1568	20000608

OTHER SOURCE(S): CASREACT 134:17731
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention concerns in all possible isomeric forms as well as their mixts., cyclic peptides I wherein: R represents a linear, branched or cyclic chain; either R1 represents H or CH3 and R2 represents cyclohexyl substituted by an amine, cyanoalkyl ; or R1 and R2 form with the nitrogen which bears them a cycle with 3, 4 or 5 carbons optionally substituted by an amine; R3 represents hydrogen, Me or hydroxyl; R4 represents hydrogen or hydroxyl; T represents hydrogen, Me, CH2CONH2, CH2CN, a (CH2)2NH2 or (CH2)2Nalk+X- radical, X being halogen and alk an alkyl radical; Y represents hydrogen, hydroxyl, halogen or OSO3H; W represents H or OH; Z represents H, CH3. The compds. of formula I have antifungal properties. Thus,. Trans 1-[4-[(2-aminocyclohexyl)amino]-N2-[[4''-(pentyloxy)[1,1':4',1''terphenyl]-4-yl]carbonyl]-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandine B trifluoroacetate was prepared and tested for its inhibition of glucan synthase of Candida albicans and of the enzyme prepared from Aspergillus fumigatus.

IC ICM C07K007-56
ICS A61K038-12; A61P031-10

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 7, 10, 63

ST echinocandin cyclic peptide prepn antifungal glucan synthase inhibitor

IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)

(cyclic; echinocandin derivs., method for preparing same and application as glucan synthase inhibitors and antifungal agents)

IT Aspergillus fumigatus
Fungicides
(echinocandin derivs., method for preparing same and application as glucan synthase inhibitors and antifungal agents)

IT 9027-19-4, Glucan synthase
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(Candida albicans; echinocandin derivs., method for preparing same and application as glucan synthase inhibitors and antifungal agents)

IT 310461-86-0P 310461-89-3P 310461-95-1P 310461-97-3P
310461-99-5P 310462-01-2P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(echinocandin derivs., method for preparing same and application as glucan synthase inhibitors and antifungal agents)

IT 538-75-0, N,N'-Dicyclohexylcarbodiimide 771-61-9,
2,3,4,5,6-Pentafluorophenol 5805-57-2, 2-(Aminomethyl)benzimidazole 19777-66-3 20439-47-8 59748-18-4
138626-63-8, Deoxymulundocandin 227472-60-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(echinocandin derivs., method for preparing same and application as glucan synthase inhibitors and antifungal agents)

IT 160430-95-5P 227472-53-9P 227472-54-0P 227472-55-1P
340020-20-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(echinocandin derivs., method for preparing same and application as glucan synthase inhibitors and antifungal agents)

REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 8 OF 27 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 133:43811 MARPAT
TITLE: Preparation of cyclic peptides as antifungal and antiparasitic agents
INVENTOR(S): Rodriguez, John Michael; Jamison, James Andrew
PATENT ASSIGNEE(S): Eli Lilly and Co., USA
SOURCE: PCT Int. Appl., 49 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000035944	A1	20000622	WO 1999-US29914	19991215

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ,

VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

EP 1140991	A1	20011010	EP 1999-966324	19991215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002535248	T2	20021022	JP 2000-588201	19991215
PRIORITY APPLN. INFO.:			US 1998-112434P	19981216
			WO 1999-US29914	19991215

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Cyclic peptides I [R = alkyl, alkenyl, alkynyl, aryl, or heteroaryl; R1 = H, OH, or O-Pg (Pg = protective group); R2 = H, Me, NH2, NH-Pg; R3 = H, Me, CH2CONH2, CH2CONH-Pg, CH2CH2NH2, or CH2CH2NH-Pg; R5 = OH, OSO3H, or OPO2HRa, where Ra = OH, alkyl, alkoxy, (un)substituted Ph, phenoxy, benzyl, or benzyloxy; R6 = H, OH, or OSO3H; R7 = H, Me; R4, R8 = H, OH and one of R4 and R8 is a sugar moiety] were prepared as antifungal and antiparasitic agents. Thus, acylation of A-30912A (echinocandin B) nucleus with [4''-(pentyloxy)-1,1':4',1''-tetraphenyl]-4-carboxylic acid 2,4,6-trichlorophenyl ester and stirring the product with 4-acetoglucosyl-2-butenol and p-toluenesulfonic acid in dioxane for 4 h afforded 12.4 g of the compound II [R = (p-C6H4)3-OCH2Bu; R8 = 4-acetoglucosyl-2-butenyl].

IC ICM C07K007-56
ICS A61K038-12; C07H007-00

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 10, 33, 63

ST cyclic peptide carbohydrate deriv prepn antifungal antiparasitic; A30912A analog prepn antifungal antiparasitic; echinocandin B analog prepn antifungal antiparasitic

IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(cyclic; preparation of cyclic glycopeptides as antifungal agents)

IT Aspergillus fumigatus
Candida albicans
Candida parapsilosis
Fungicides
Parasiticides
Pneumocystis carinii
(preparation of cyclic glycopeptides as antifungal agents)

IT Glycopeptides
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of cyclic peptides as antifungal agents)

IT 572-09-8, Acetobromoglucose 2595-05-3, 1,2,5,6-Diacetone-D-allofuranose 2873-29-2, Tri-acetyl-D-glucal 3615-41-6, L-Rhamnose 6117-80-2, (Z)-2-Butene-1,4-diol 7658-08-4,

6-Deoxyglucose 13100-46-4, 1,2,3,4-Tetra-O-acetyl-β-D-glucopyranose 54651-05-7, Echinocandin B 158937-65-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of cyclic glycopeptides as antifungal agents)

IT 7468-48-6P 13964-21-1P 17081-04-8P 108942-38-7P 120878-44-6P 130678-92-1P 166663-25-8P 191668-77-6P 240141-38-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of cyclic glycopeptides as antifungal agents)

IT 276255-72-2P
RL: RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of cyclic glycopeptides as antifungal agents)

IT 276255-73-3P 276255-74-4P 276255-75-5P 276255-76-6P 276255-77-7P 276255-78-8P 276255-79-9P 276255-80-2P 276255-81-3P
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of cyclic glycopeptides as antifungal agents)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 9 OF 27 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 133:42250 MARPAT
TITLE: Purification of echinocandin cyclopeptide compounds
INVENTOR(S): Dobbins, John Robert; Kroeff, Eugene Paul; Vicenzi, Jeffrey Thomas
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000034315	A2	20000615	WO 1999-US29008	19991208
WO 2000034315	A3	20001228		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1137663	A2	20011004	EP 1999-965156	19991208
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
BR 9916101	A	20020604	BR 1999-16101	19991208
ZA 2001004621	A	20020606	ZA 2001-4621	20010606
US 6506726	B1	20030114	US 2001-857924	20011210
PRIORITY APPLN. INFO.:			US 1998-111524P	19981209

WO 1999-US29008 19991208

AB A method is described for separating and purifying a wide variety of fermentation cyclopeptide products containing at least one protonatable amino group (including the deacylated echinocandin-type compds.) from their fermentation or mixed broths and partially purified process streams by adsorbing the mixture onto a hydrophobic, reversed phase chromatog. media and eluting with a continuous linear HOAc gradient ranging 0.1-10.0% by volume in water. A process for removing tripeptide-aldehyde byproducts from the fermentation products by means of a derivatizing agent is also described.

IC ICM C07K007-56

CC 16-2 (Fermentation and Bioindustrial Chemistry)

ST echinocandin purifn fermn HPLC acetate

IT Fermentation
Reversed phase HPLC
(purification of echinocandin cyclopeptide compds.)

IT 80619-41-6P, Echinocandin
RL: BMF (Bioindustrial manufacture); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation)
(purification of echinocandin cyclopeptide compds.)

IT 79411-15-7P
RL: BPN (Biosynthetic preparation); PUR (Purification or recovery); BIOL (Biological study); PREP (Preparation)
(purification of echinocandin cyclopeptide compds.)

IT 64-19-7, Acetic acid, uses
RL: NUU (Other use, unclassified); USES (Uses)
(purification of echinocandin cyclopeptide compds.)

IT 275376-21-1
RL: REM (Removal or disposal); PROC (Process)
(purification of echinocandin cyclopeptide compds.)

L33 ANSWER 10 OF 27 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 133:30961 MARPAT
TITLE: Preparation of cyclic peptide antifungal and antiparasitic agents having sugar substituent
INVENTOR(S): Rodriguez, John Michael; Nesler, Michael John; Zwelfel, Mark James
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000035945	A1	20000622	WO 1999-US29927	19991215

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW

RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA,

GN, GW, ML, MR, NE, SN, TD, TG
EP 1140992 A1 20011010 EP 1999-966327 19991215
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO
JP 2002532513 T2 20021002 JP 2000-588202 19991215
PRIORITY APPLN. INFO.: US 1998-112433P 19981216
WO 1999-US29927 19991215

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Sugar-containing cyclic peptides I wherein R is an alkyl group, an alkenyl group, an alkynyl group, an aryl group, or heteroaryl group; R1 is independently H, OH or O-Pg; Pg is a protecting group; R2 is H, CH3, NH2, or NH-Pg; R3 is H, CH3, CH2CONH2, CH2CONH-Pg, CH2CH2NH2, or CH2CH2NH-Pg; R4 is H, OH , or O-Pg; R5 is OH , OSO3H, or OPO2HRa, where Ra is hydroxy , C-C 6 alkyl , C1-C6 alkoxy, Ph , phenoxy , p-halophenyl , p-halophenoxy, p-nitrophenyl , p-nitrophenoxy , benzyl , benzyloxy , p-halobenzyl , p-halobenzyloxy , p-nitrobenzyl , or p-nitrobenzyloxy ; R6 is H, OH , or OSO3H; R7 is H or CH3; n is an integer from 2-7; R8 is a sugar moiety; were prepared as antifungal and antiparasitic agents. Thus, cyclic peptide II was prepared and tested in mice for its antifungal and antiparasitic activities. Treatment and pharmaceutical formulation of these compds. in tablets and capsules is also reported.

IC C07C007-56; A61K038-12; A61P031-10; A61P033-00

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 10, 33, 63

ST antiparasitic fungicide cyclic peptide prepn

IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclic; preparation of cyclic peptide antifungal and antiparasitic agents having sugar substituent)

IT Fungicides
Parasiticides
(preparation of cyclic peptide antifungal and antiparasitic agents having sugar substituent)

IT 273917-37-6P 273917-38-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of cyclic peptide antifungal and antiparasitic agents having sugar substituent)

IT 165668-18-8P 166663-25-8P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of cyclic peptide antifungal and antiparasitic agents having sugar substituent)

IT 2002-24-6, Ethanolamine hydrochloride 6294-16-2, α-D-Galacturonic acid 6556-12-3, D-Glucuronic acid 54651-05-7, Echinocandin B 158937-65-6

RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of cyclic peptide antifungal and antiparasitic agents having sugar substituent)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 11 OF 27 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 132:308664 MARPAT
TITLE: Photochemical process for conversion of the 1,2-diol moiety of an echinocandin compound to the 1-deoxy-2-keto analog
INVENTOR(S): Hitchcock, Stephen Andrew; Gregory, George Stuart
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 28 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000024694	A1	20000504	WO 1999-US25301	19991027

W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1998-105936P 19981028
OTHER SOURCE(S): CASREACT 132:308664

AB A method for converting an epoxy or hydroxy moiety to a 1-deoxy-2-keto moiety is described which includes: (1) reacting a compound having an epoxy or hydroxy moiety with a thiophenol and (2) irradiating the 1-phenylthio-2-hydroxy moiety with UV or near-UV radiation to convert the 1-phenylsulfide-2-hydroxy moiety to a 1-deoxy-2-keto moiety. The process was used to modify the cyclic peptide ring system of an echinocandin-type compound containing a 1,2-diol moiety to produce new keto analogs.

IC ICM C07B041-06
ICS C07K007-56
CC 34-3 (Amino Acids, Peptides, and Proteins)
ST echinocandin diol conversion deoxy keto analog; keto analog echinocandin prepn
IT Peptides, preparation
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclic; photochem. process for conversion of diol moiety of an echinocandin compound to 1-deoxy-2-keto analog)
IT 266317-26-4P
RL: IMF (Industrial manufacture); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)

(photochem. process for conversion of diol moiety of an echinocandin compound to 1-deoxy-2-keto analog)

IT 266317-27-5P 266317-28-6P
RL: IMF (Industrial manufacture); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(photochem. process for conversion of diol moiety of an echinocandin compound to 1-deoxy-2-keto analog)

IT 119-26-6, 2,4-Dinitrophenylhydrazine 1099-45-2, Ethyl triphenylphosphoranylideneacetate 37972-89-7, Benzenethiol, 2-iodo- 166663-25-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(photochem. process for conversion of diol moiety of an echinocandin compound to 1-deoxy-2-keto analog)

IT 266317-25-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(photochem. process for conversion of diol moiety of an echinocandin compound to 1-deoxy-2-keto analog)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 12 OF 27 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 132:208137 MARPAT
TITLE: Reversible boronate complexes of 1,2-cis-diol cyclic peptides
INVENTOR(S): Moser, Brian Allen; Baker, Jeffrey Clayton
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 35 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000012540	A1	20000309	WO 1999-US19066	19990818
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2340647	AA	20000309	CA 1999-2340647	19990818
AU 9956834	A1	20000321	AU 1999-56834	19990818
AU 763351	B2	20030717		
EP 1107982	A1	20010620	EP 1999-943807	19990818
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.: US 1998-98267P 19980828
WO 1999-US19066 19990818

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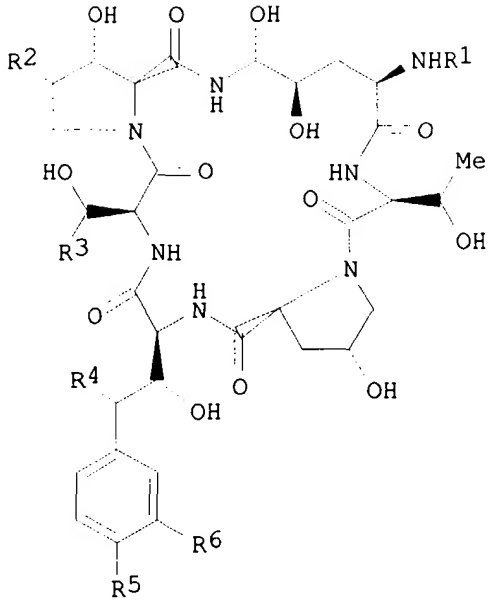

I

AB Reversible borate or boronate complexes of 1,2-cis-diol cyclic peptides are useful for purification, isolation, stabilization and/or water solubilization of their resp. parent 1,2-cis-diol cyclic peptides I (R1 = H, acyl; R2 = H, Me; R3 = H, Me, CH2CONH2, CH2CH2NH2; R4 = H, OH; R5 = OH, OPO3H2, OSO3H; R6 = H, OSO3H). The method is particularly useful for forming boronate adducts of hydrophobic echinocandin compds. to increase their water solubility Thus, the solubility of I (R1 = p-pentyloxy-p-terphenylcarbonyl; R2, R3 = Me; R4, R6 = H; R5 = OH) was increased in the presence of m-aminophenylboronic acid (concentration 23.76 mg/mL in supernatant or 94% of the original suspension, vs. 2.27 mg/mL in ammonium bicarbonate control supernatant).

IC ICM C07K007-56
ICS A61K038-12

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 29

ST echinocandin cyclic peptide solubilization boronate complex

IT Peptides, reactions
RL: RCT (Reactant); RACT (Reactant or reagent)
(cyclic; reversible boronate complexes of cis-diol cyclic peptides)

IT 98-80-6, Phenylboronic acid 1765-93-1, p-Fluorophenylboronic acid 4151-80-8 4347-33-5 4426-47-5, Butylboronic acid 4433-63-0, Ethylboronic acid 5467-74-3, p-Bromophenylboronic acid 5720-05-8, p-Methylphenylboronic acid 5720-07-0, p-Methoxyphenylboronic acid 6165-68-0, 2-Thiopheneboronic acid 6165-69-1, 3-Thiopheneboronic acid 13922-41-3, 1-Naphthylboronic acid 14047-29-1, p-Carboxyphenylboronic acid 16419-60-6, o-Methylphenylboronic acid 17745-45-8, Propylboronic acid 24067-17-2, p-Nitrophenylboronic acid 30418-59-8,

m-Aminophenylboronic acid 40138-16-7, o-Formylphenylboronic acid 87199-16-4, m-Formylphenylboronic acid 98437-23-1, Benzo[b]thiophene-2-boronic acid 98437-24-2 103681-98-7 128796-39-4 144104-59-6 162607-18-3 206551-43-1 260368-77-2 260369-10-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(reversible boronate complexes of cis-diol cyclic peptides)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 13 OF 27 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 132:194661 MARPAT
TITLE: Preparation of ring modified cyclic peptide analogs as antifungal agents
INVENTOR(S): Borromeo, Peter Stanley; Cohen, Jeffrey Daniel; Gregory, George Stuart; Henle, Stacy Kay; Hitchcock, Stephen Andrew; Jungheim, Louis Nickolaus; Mayhugh, Daniel Ray; Shepherd, Timothy Alan; Turner, William Wilson, Jr.
PATENT ASSIGNEE(S): Eli Lilly and Company, USA
SOURCE: PCT Int. Appl., 108 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000011023	A2	20000302	WO 1999-US18908	19990818
WO 2000011023	A3	20000615		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, HR, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2340676	AA	20000302	CA 1999-2340676	19990818
AU 9955726	A1	20000314	AU 1999-55726	19990818
EP 1107981	A2	20010620	EP 1999-942321	19990818
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
JP 2002528388	T2	20020903	JP 2000-566295	19990818
PRIORITY APPLN. INFO.:			US 1998-97228P	19980820
			WO 1999-US18908	19990818

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB A method is provided for modifying the cyclic peptide ring system of echinocandin-type compds. to produce new analogs, e.g., I (R =

alkyl, alkenyl, alkynyl, aryl, heteroaryl; R1, R4 = H, OH; R2 = H, Me; R3 = H, Me, CH2CONH2, CH2, CH2NH2; R5 = OH, OPO3H2, OSO3H; R6 = H, OSO3H), having antifungal activity. The process comprises opening the cyclic peptide ring, cleaving the terminal ornithine unit, inserting at least one new amino acid or other synthetic unit and closing the ring to produce a new cyclic peptide ring structure. Thus, cyclic peptide II [R = p-(pentyloxy)-p-terphenyl] was prepared and showed min. inhibitory concns. 0.005-0.156 μg/mL against four fungi.

IC ICM C07K007-50
ICS A61K038-12

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 10

ST cyclic peptide prepn fungicide

IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclic; preparation of ring modified cyclic peptide analogs as antifungal agents)

IT Emulsifying agents
Flavoring materials
Fungicides
Lubricants
Perfumes
Preservatives
Stabilizing agents
Sweetening agents
Wetting agents
(preparation of ring modified cyclic peptide analogs as antifungal agents)

IT 259824-88-9P 259825-07-5P 259825-57-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of ring modified cyclic peptide analogs as antifungal agents)

IT 259824-75-4P 259824-76-5P 259824-77-6P 259824-78-7P
259824-79-8P 259824-89-0P 259824-91-4P 259824-92-5P
259824-93-6P 259824-94-7P 259824-95-8P 259824-96-9P
259824-97-0P 259825-08-6P 259825-17-7P 259825-30-4P
259825-36-0P 259825-41-7P 259825-42-8P 259825-43-9P
259825-44-0P 259825-45-1P 259825-46-2P 259825-47-3P
259825-48-4P 259825-49-5P 259825-58-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of ring modified cyclic peptide analogs as antifungal agents)

IT 50-00-0, Formaldehyde, reactions 75-07-0, Acetaldehyde, reactions 103-72-0, Phenyl isothiocyanate 123-38-6, Propionaldehyde, reactions 672-15-1, L-Homoserine 2389-45-9 2480-93-5 16937-92-1 25508-20-7 56926-94-4 65621-26-3 65710-57-8 68642-94-4 79404-91-4, Cilofungin 118554-00-0 252049-08-4
RL: RCT (Reactant); RACT (Reactant or reagent)

(preparation of ring modified cyclic peptide analogs as antifungal agents)

IT 16748-79-1P 30925-18-9P 62234-36-0P 62234-37-1P 76387-70-7P
85003-76-5P 259824-65-2P 259824-67-4P 259824-68-5P
259824-69-6P 259824-70-9P 259824-72-1P 259824-73-2P
259824-74-3P 259824-80-1P 259824-81-2P 259824-82-3P
259824-83-4P 259824-84-5P 259824-85-6P 259824-86-7P
259824-87-8P 259824-98-1P 259824-99-2P 259825-00-8P
259825-01-9P 259825-02-0P 259825-03-1P 259825-04-2P
259825-05-3P 259825-06-4P 259825-09-7P 259825-10-0P
259825-11-1P 259825-12-2P 259825-14-4P 259825-16-6P
259825-20-2P 259825-22-4P 259825-24-6P 259825-25-7P
259825-27-9P 259825-29-1P 259825-31-5P 259825-32-6P
259825-33-7P 259825-34-8P 259825-35-9P 259825-37-1P
259825-38-2P 259825-39-3P 259825-40-6P 259825-50-8P
259825-51-9P 259825-52-0P 259825-53-1P 259825-54-2P
259825-55-3P 259825-56-4P 259825-59-7P 259825-60-0P
259825-61-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of ring modified cyclic peptide analogs as antifungal agents)

L33 ANSWER 14 OF 27 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 131:144853 MARPAT
TITLE: Cyclic hexapeptides having antimicrobial activity
INVENTOR(S): Ohki, Hidenori; Murano, Kenji; Tojo, Takashi; Shiraishi, Nobuyuki; Matsuya, Takahiro; Matsuda, Hiroshi; Mizuno, Hiroaki; Barrett, David; Matsuda, Keiji; Kawabata, Kohji
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan; et al.
SOURCE: PCT Int. Appl., 470 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9940108	A1	19990812	WO 1999-JP538	19990205
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
CA 2320416	AA	19990812	CA 1999-2320416	19990205
AU 9922998	A1	19990823	AU 1999-22998	19990205
AU 756792	B2	20030123		
BR 9907967	A	20001017	BR 1999-7967	19990205
EP 1053247	A1	20001122	EP 1999-902855	19990205
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				

JP 2001522377	T2	20011113	JP 1999-540287	19990205
ZA 9900985	A	19990810	ZA 1999-985	19990208
US 6232290	B1	20010515	US 1999-446101	19991222
NO 2000003996	A	20001009	NO 2000-3996	20000808
PRIORITY APPLN. INFO.:			AU 1998-1728	19980209
			AU 1998-3138	19980423
			WO 1999-JP538	19990205

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Polypeptides I [R1 = H, (un)substituted arylaminoalkanoyl, aroyl, arylalkanoyl, or alkanoyl, amino protective group, heptylnaphthoyl, hexylnaphthoyl; R2 = H, OH; R3 = OH, hydroxysulfonyloxy, alkoxy; R4 = OH, alkoxy] or their salts were prepared as antimicrobial activities (especially, antifungal activities). Thus, cyclic peptide II, prepared via N-acylation using 4-[5-[4-(6-methoxyhexyloxy)phenyl]-1,3,4-thiadiazol-2-yl]benzoic acid benzotriazol-1-yl ester, showed MIC 0.0625 μg/mL for inhibition of Candida albicans.

IC ICM C07K007-56
ICS A61K038-12

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 10

ST cyclic peptide prepn antimicrobial; antifungal cyclic peptide

IT Antimicrobial agents
Fungicides
(cyclic hexapeptides having antimicrobial activity)

IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclic; cyclic hexapeptides having antimicrobial activity)

IT 235112-67-1P 235112-73-9P 235112-76-2P 235112-86-4P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(cyclic hexapeptides having antimicrobial activity)

IT 235112-75-1P 235112-77-3P 235112-78-4P 235112-79-5P
235112-80-8P 235112-81-9P 235112-82-0P 235112-83-1P
235112-84-2P 235112-85-3P 235112-87-5P 235112-88-6P
235112-89-7P 235112-90-0P 235112-91-1P 235112-92-2P
235112-93-3P 235112-94-4P 235112-95-5P 235112-96-6P
235112-97-7P 235112-98-8P 235112-99-9P 235113-00-5P
235113-01-6P 235113-02-7P 235113-03-8P 235113-04-9P
235113-05-0P 235113-06-1P 235113-07-2P 235113-08-3P
235113-09-4P 235113-10-7P 235113-11-8P 235113-12-9P
235113-13-0P 235113-14-1P 235113-15-2P 235113-16-3P
235113-17-4P 235113-18-5P 235113-19-6P 235113-20-9P
235113-21-0P 235113-22-1P 235113-23-2P 235113-24-3P
235113-25-4P 235113-26-5P 235113-27-6P 235113-28-7P
235113-29-8P 235113-30-1P 235113-31-2P 235113-32-3P
235113-33-4P 235113-34-5P 235113-35-6P 235113-36-7P
235113-37-8P 235113-38-9P 235113-39-0P 235113-40-3P

235113-41-4P 235113-42-5P 235113-43-6P 235113-44-7P
235113-45-8P 235113-46-9P 235113-47-0P 235113-48-1P
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235432-54-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclic hexapeptides having antimicrobial activity)

IT 79-19-6, Thiosemicarbazide 99-76-3, 4-Hydroxybenzoic acid methyl ester 99-93-4, 4-Hydroxyacetophenone 106-53-6, 4-Bromobenzenethiol 108-93-0, Cyclohexanol, reactions 109-65-9, Butyl bromide 109-86-4, 2-Methoxyethanol 110-52-1, 1,4-Dibromobutane 110-53-2, 1-Bromopentane 110-89-4, Piperidine, reactions 111-24-0, 1,5-Dibromopentane 112-29-8, 1-Bromodecane 456-64-4, n-Phenyltrifluoromethanesulfonamide 588-63-6, 3-Phenoxypropyl bromide 589-15-1, 4-Bromobenzyl bromide 589-92-4, 4-Methylcyclohexanone 629-03-8, 1,6-Dibromohexane 870-46-2, tert-Butyl carbazate 1200-03-9, 4-Phenoxybutyl bromide 1521-51-3 2592-95-2, 1-Hydroxybenzotriazole 4254-29-9, 2-Indanol 4549-31-9, 1,7-Dibromoheptane 5467-72-1, 2-Amino-4'-bromoacetophenone hydrochloride 6485-55-8, cis-2,6-Dimethylmorpholine 7377-26-6, 4-Methoxycarbonylbenzoyl chloride 13188-55-1 15872-42-1 19438-10-9, 3-Hydroxybenzoic acid methyl ester 39512-49-7 51105-90-9 57260-71-6 58574-03-1 73781-91-6, Methyl 6-chloronicotinate 79099-07-3, n-tert-Butoxycarbonyl-4-piperidinone 81590-55-8, Ethyl 4-bromoacetylbenzoate 93467-67-5 99768-12-4, 4-Methoxycarbonylphenylboronic acid 101038-65-7 138328-74-2 141518-06-1 158098-97-6 168110-44-9 208537-80-8 235112-69-3 235112-71-7 235112-72-8 235112-74-0 235114-35-9 235114-36-0 235114-37-1 235114-38-2 235114-39-3 235114-40-6 235114-41-7 235114-42-8 235114-43-9 235114-44-0 235114-45-1 235114-46-2 235114-47-3 235114-48-4 235114-49-5 235114-50-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(cyclic hexapeptides having antimicrobial activity)

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RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);

RACT (Reactant or reagent)
(cyclic hexapeptides having antimicrobial activity)

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RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);

RACT (Reactant or reagent)
(cyclic hexapeptides having antimicrobial activity)
REFERENCE COUNT: 2 THERE ARE 2 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 15 OF 27 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 131:45105 MARPAT
TITLE: Preparation of Echinocandin B derivatives as antifungal agents
INVENTOR(S): Courtin, Olivier; Fauveau, Patrick; Markus, Astrid; Melon Manguer, Dominique; Michel, Jean-Marc; Schio, Laurent
PATENT ASSIGNEE(S): Hoechst Marion Roussel, Fr.
SOURCE: PCT Int. Appl., 46 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9929716	A1	19990617	WO 1998-FR2671	19981209
W: AL, AU, BA, BB, BG, BR, CA, CN, CU, CZ, EE, GD, GE, HR, HU, ID, IL, IN, IS, JP, KP, KR, LC, LK, LR, LT, LV, MG, MK, MN, MX, NO, NZ, PL, RO, SG, SI, SK, SL, TR, TT, UA, US, UZ, VN, YU, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
FR 2772028	A1	19990611	FR 1997-15628	19971210
FR 2772028	B1	20000204		
FR 2784993	A1	20000428	FR 1998-13361	19981026
FR 2784993	B1	20021031		
ZA 9811158	A	19991207	ZA 1998-11158	19981207
CA 2311295	AA	19990617	CA 1998-2311295	19981209
AU 9915659	A1	19990628	AU 1999-15659	19981209
AU 755033	B2	20021128		
EP 1036090	A1	20000920	EP 1998-959935	19981209
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, SI, LT, LV, FI, RO				
BR 9813531	A	20001010	BR 1998-13531	19981209
EE 200000336	A	20010815	EE 2000-200000336	19981209
JP 2001525421	T2	20011211	JP 2000-524307	19981209
NZ 504614	A	20021220	NZ 1998-504614	19981209
TW 446541	B	20010721	TW 1998-87121185	19990122
BG 104494	A	20010131	BG 2000-104494	20000531
NO 2000002959	A	20000809	NO 2000-2959	20000609
HR 2000000384	A1	20001031	HR 2000-384	20000609
PRIORITY APPLN. INFO.:			FR 1997-15628	19971210
			FR 1998-13361	19981026
			WO 1998-FR2671	19981209

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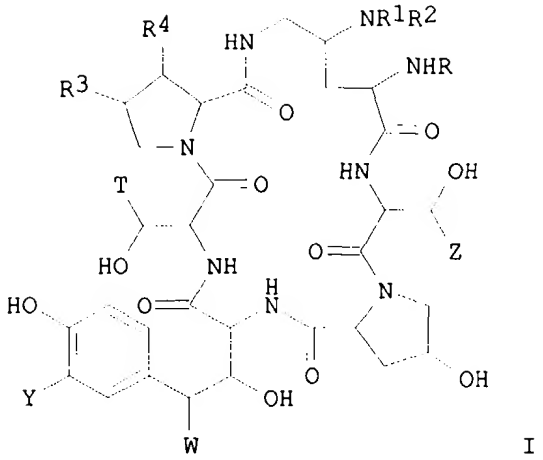

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AB The title compds. I (R1, R2 = H, OH, (substituted) alkyl, NR1 forms with the carbon bearing NR1R2 a double bond and R2 = MP; M = O, NH, alkylamino; P = H, (substituted) alkyl; R3 = H, OH, CH3; R4 = H, OH; R = linear or branched chain up to 30 carbon atoms optionally substituted with heteroatoms, aryls or heterocycles; T = H, CH3, CH2CONH2, CH2C.tplbond.N, (CH2)2NH2; Y = H, OH, halogen; W = H, OH; Z = H, CH3) were prepared as antifungal agents (no data given). For example, 1-[(4R,5R)-4,5-dihydroxy-N2-(12-methyltetradecanoyl)-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B was treated with trimethylsilyl iodide and sodium thiosulfate in succession to give the intermediate 1-[N2-(12-methyltetradecanoyl)-4-oxo-L-ornithine]-4-[4-(4-hydroxyphenyl)-L-threonine]-5-L-serine-echinocandin B in 62% yield. This intermediate, when treated with 2-(dimethylamino)ethylamine, gave the final product I [NR1R2 = NHCH2CH2NMe2, R = CO(CH2)10CH(CH3)CH2CH3, Z = CH3, W = Y = T = H, R3 = CH3, R4 = OH] as a mixture of isomers, which were, then, separated via HPLC.

IC ICM C07K007-56
ICS A61K038-12

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1

ST echinocandin B deriv prepn antifungal agent

IT Fungicides
(preparation of echinocandin derivs. as antifungal agents)

IT 227472-27-7P 227472-67-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of echinocandin derivs. as antifungal agents)

IT 227472-29-9P 227472-31-3P 227472-33-5P 227472-34-6P
227472-35-7P 227472-37-9P 227472-38-0P 227472-39-1P
227472-40-4P 227472-41-5P 227472-42-6P 227472-43-7P
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227472-72-2P 227472-73-3P 227472-74-4P
RL: BAC (Biological activity or effector, except adverse); BSU

(Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of echinocandin derivs. as antifungal agents)

IT 107-15-3, 1,2-Ethanediamine, reactions 108-00-9, 2-(Dimethylamino)ethylamine 109-76-2, 1,3-Diaminopropane 1937-19-5 3279-95-6 55959-84-7 59748-18-4 65920-18-5 227472-53-9 227472-57-3 227614-36-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of echinocandin derivs. as antifungal agents)

IT 138626-63-8P, Deoxymulundocandin 160430-95-5P 227472-52-8P 227472-54-0P 227472-55-1P 227472-56-2P 227472-58-4P 227472-59-5P 227472-60-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of echinocandin derivs. as antifungal agents)

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 16 OF 27 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 130:25351 MARPAT
TITLE: Preparation of new echinocandide derivatives with antimicrobial activity
INVENTOR(S): Hori, Yasuhiro; Tsurumi, Yasuhisa; Takase, Shigehiro; Hatanaka, Hiroshi; Sakamoto, Kazutoshi; Hashimoto, Seiji; Ohki, Hidenori; Tojo, Takashi; Matsuda, Keiji; Kawabata, Kohji
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan; et al.
SOURCE: PCT Int. Appl., 91 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9852967	A1	19981126	WO 1998-JP2168	19980518
W: BR, CA, CN, JP, KR, US				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 983297	A1	20000308	EP 1998-919630	19980518
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2002502239	T2	20020122	JP 1998-550222	19980518
US 6331521	B1	20011218	US 1999-423654	19991201
PRIORITY APPLN. INFO.:			AU 1997-6918	19970521
			WO 1998-JP2168	19980518

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The invention relates to new echinocandide derivs. I [R1 = H, acyl;, R2 = H, OH; R3 = H, Me; R4 = H, OH; with the proviso that when R4 = OH, R2 = OH] or a salt thereof which have antimicrobial activities

(especially antifungal activities), inhibitory activity on β-1,3-glucan synthase, to process for preparation thereof, to a pharmaceutical composition comprising the same, and to a method for the prophylactic and/or therapeutic treatment of infectious diseases including Pneumocystis carinii infection (e.g. Pneumocystis carinii pneumonia) in a human being or an animal. Thus, echinocandin derivative II [R = CO(CH2)14Me] (WF 738B), isolated from a culture of Coleophoma carterformis Number 738, was deacylated by treatment with washed mycelium of Actinoplanes utahensis IFO-13244 to give deacyl derivative II (R = H). Acylation of II (R = H) with a variety of activated benzoic acid derivs. gave modified title compds., e.g. II [R = 4-COC6H4-X-C6H4O(CH2)nMe-4; X = bond, 1,4-piperazinediyl, 3,5-isoxazoldiyl, 1,3,4-thiadiazol-2,5-diyl, thiazol-5,2-diyl, thiazol-2,5-diyl; n = 2,4,5,7].

IC ICM C07K007-56
ICS A61K038-04; C12P021-02; C12N001-14; C12P021-02; C12R001-645; C12N001-14; C12R001-645

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 10, 16

ST echinocandin deriv prepn antibacterial agent; acylation deacylated echinocandin deriv antibacterial agent; Coleophoma crateriformis 738 echinocandin isolation

IT Coleophoma crateriformis
(Number 738; preparation of new echinocandide derivs. with antimicrobial activity)

IT Antibacterial agents
(preparation of new echinocandide derivs. with antimicrobial activity)

IT 216493-58-2P, WF 738A 216493-59-3P, WF 738B 216493-60-6P, WF 738C
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(preparation of new echinocandide derivs. with antimicrobial activity)

IT 216311-94-3P 216311-96-5P 216311-97-6P 216311-98-7P
216311-99-8P 216312-00-4P 216312-01-5P 216312-02-6P
216312-03-7P 216312-04-8P 216312-06-0P 216312-08-2P
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of new echinocandide derivs. with antimicrobial activity)

IT 216311-92-1P 216312-10-6P 216312-12-8P 216312-14-0P
216493-61-7P, WF 738D2
RL: BPN (Biosynthetic preparation); RCT (Reactant); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of new echinocandide derivs. with antimicrobial activity)

IT 111-25-1, n-Hexyl bromide 1679-64-7, Terephthalic acid monomethyl ester 7644-04-4 15872-41-0, 4-Pentyloxybenzoic acid
40513-43-7, 2-Amino-4'-methoxyacetophenone 59748-13-9 81590-55-8
216312-48-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of new echinocandide derivs. with antimicrobial activity)

IT 108783-61-5P 193813-77-3P 216312-16-2P 216312-18-4P
216312-20-8P 216312-22-0P 216312-24-2P 216312-26-4P
216312-28-6P 216312-30-0P 216312-32-2P 216312-34-4P
216312-37-7P 216312-39-9P 216312-41-3P 216312-43-5P
216312-44-6P 216312-45-7P 216312-46-8P 216312-47-9P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of new echinocandide derivs. with antimicrobial activity)
REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 17 OF 27 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 129:54604 MARPAT
TITLE: Cyclohexapeptides having antimicrobial activity
INVENTOR(S): Ohki, Hidenori; Tomishima, Masaki; Yamada, Akira; Takasugi, Hisashi
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan; Ohki, Hidenori; Tomishima, Masaki; Yamada, Akira; Takasugi, Hisashi
SOURCE: PCT Int. Appl., 115 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9823637	A1	19980604	WO 1997-JP4193	19971118
W: CA, CN, JP, KR, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 941236	A1	19990915	EP 1997-912494	19971118
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
JP 2001505880	T2	20010508	JP 1998-524500	19971118
US 2002193560	A1	20021219	US 1999-308237	19990521
PRIORITY APPLN. INFO.:			AU 1996-3814	19961125
			WO 1997-JP4193	19971118

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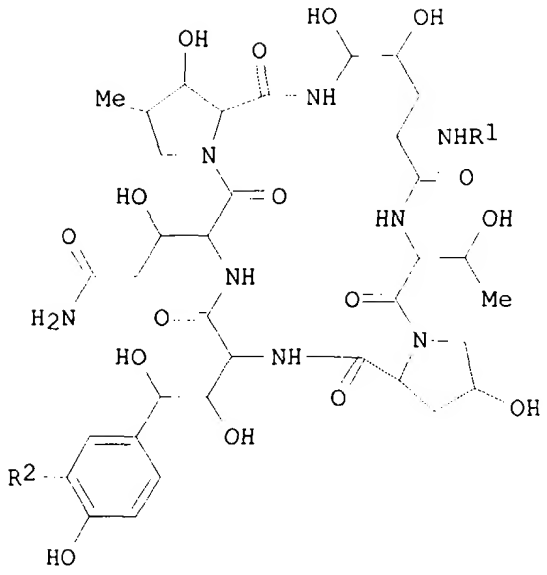

I

AB Polypeptide compds. I [R1 = (un)substituted aroyl or alkanoyl; R2 = OH, HO3SO, alkoxy] or their salts were prepared as antimicrobial agents. Thus, I [R1 = 4-[4-(4-hexyloxyphenyl)piperazin-1-yl]benzoyl, R2 = NaOSO2O] was prepared by treating I [R1 = H, R2 = NaOSO2O] with 1-[4-[4-(4-hexyloxyphenyl)piperazin-1-yl]benzoyloxy]benzotriazole for 8 h in DMF containing diisopropylethylamine.

IC ICM C07K007-56
ICS A61K038-12

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 10

ST cyclic peptide prepn antimicrobial

IT Peptides, preparation
RL: SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclohexapeptides; preparation of cyclohexapeptides having antimicrobial activity)

IT Antimicrobial agents
(preparation of cyclohexapeptides having antimicrobial activity)

IT 179165-67-4P 208538-36-7P 208538-37-8P 208538-38-9P
208538-39-0P 208538-40-3P 208538-41-4P 208538-42-5P
208538-43-6P 208538-44-7P 208538-45-8P 208538-46-9P
208538-47-0P 208538-48-1P 208538-49-2P 208538-50-5P
208538-51-6P 208538-53-8P 208538-54-9P 208538-55-0P
208538-56-1P 208538-57-2P 208538-58-3P 208538-59-4P
208538-61-8P 208538-63-0P 208538-65-2P 208538-67-4P
208538-78-7P 208663-11-0P 208663-12-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of cyclohexapeptides having antimicrobial activity)

IT 208537-48-8P

RL: BYP (Byproduct); PREP (Preparation)
(preparation of cyclohexapeptides having antimicrobial activity)

IT 70-23-5, Ethyl bromopyruvate 92-68-2, 4-Cyclohexylcyclohexanone 92-92-2, [1,1'-Biphenyl]-4-carboxylic acid 108-85-0, Bromocyclohexane 1571-08-0, Methyl 4-formylbenzoate 2592-95-2, 1h-Benzotriazol-1-ol 4568-71-2 5798-75-4, Ethyl 4-bromobenzoate 15872-41-0, 4-Pentyloxybenzoic acid 19099-93-5, 1-Benzyloxycarbonyl-4-piperidone 25495-91-4, Bromohexane 30752-19-3 58574-03-1 65787-72-6 67914-60-7 68749-95-1 79887-16-4, (4-Pentyloxyphenyl)acetylene 80518-57-6, 1-(4-Ethoxycarbonylphenyl)piperazine 81590-55-8, Ethyl 4-bromoacetylbenzoate 179164-78-4 208538-32-3 208538-33-4 208538-69-6 208538-71-0 208538-73-2 208538-75-4 208538-76-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of cyclohexapeptides having antimicrobial activity)

IT 70057-66-8P 95979-80-9P 149554-15-4P 158098-97-6P 179165-00-5P 187834-88-4P 208537-20-6P 208537-21-7P 208537-22-8P 208537-23-9P 208537-25-1P 208537-26-2P 208537-27-3P 208537-28-4P 208537-29-5P 208537-30-8P 208537-31-9P 208537-32-0P 208537-33-1P 208537-34-2P 208537-35-3P 208537-36-4P 208537-37-5P 208537-38-6P 208537-39-7P 208537-40-0P 208537-41-1P 208537-42-2P 208537-43-3P 208537-44-4P 208537-45-5P 208537-46-6P 208537-47-7P 208537-49-9P 208537-50-2P 208537-51-3P 208537-52-4P 208537-53-5P 208537-54-6P 208537-55-7P 208537-56-8P 208537-57-9P 208537-58-0P 208537-59-1P 208537-60-4P 208537-61-5P 208537-62-6P 208537-63-7P 208537-64-8P 208537-65-9P 208537-66-0P 208537-67-1P 208537-68-2P 208537-69-3P 208537-70-6P 208537-71-7P 208537-72-8P 208537-73-9P 208537-74-0P 208537-75-1P 208537-76-2P 208537-77-3P 208537-78-4P 208537-79-5P 208537-80-8P 208537-81-9P 208537-82-0P 208537-83-1P 208537-84-2P 208537-85-3P 208537-86-4P 208537-87-5P 208537-88-6P 208537-89-7P 208537-90-0P 208537-91-1P 208537-92-2P 208537-93-3P 208537-94-4P 208537-95-5P 208537-96-6P 208537-97-7P 208537-98-8P 208537-99-9P 208538-00-5P 208538-01-6P 208538-02-7P 208538-03-8P 208538-04-9P 208538-05-0P 208538-06-1P 208538-07-2P 208538-08-3P 208538-09-4P 208538-10-7P 208538-12-9P 208538-13-0P 208538-14-1P 208538-15-2P 208538-16-3P 208538-18-5P 208538-20-9P 208538-21-0P 208538-22-1P 208538-23-2P 208538-24-3P 208538-25-4P 208538-26-5P 208538-27-6P 208538-28-7P 208538-29-8P 208538-30-1P 208538-31-2P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of cyclohexapeptides having antimicrobial activity)

REFERENCE COUNT: 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L33 ANSWER 18 OF 27 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 128:85831 MARPAT
TITLE: Cyclic lipopeptide acylase of Oidiodendron or Verticillium for deacylation of cyclic lipopeptide FR901379
INVENTOR(S): Ueda, Satoshi; Tanaka, Miho; Ezaki, Masami; Sakamoto, Kazutoshi; Hashimoto, Seiji; Oohata,

Nobutaka; Tsuboi, Masaru; Yamashita, Michio
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan; Ueda, Satoshi; Tanaka, Miho; Ezaki, Masami; Sakamoto, Kazutoshi; Hashimoto, Seiji; Oohata, Nobutaka; Tsuboi, Masaru; Yamashita, Michio

SOURCE: PCT Int. Appl., 51 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9747738	A1	19971218	WO 1997-JP2003	19970611
W: CA, CN, JP, KR, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
EP 933422	A1	19990804	EP 1997-926214	19970611
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
US 6146872	A	20001114	US 1998-147352	19981231
US 6372474	B1	20020416	US 2000-659335	20000912
US 2002115133	A1	20020822	US 2002-50150	20020118

PRIORITY APPLN. INFO.:
JP 1996-151948 19960613
WO 1997-JP2003 19970611
US 1998-147352 19981231
US 2000-659335 20000912

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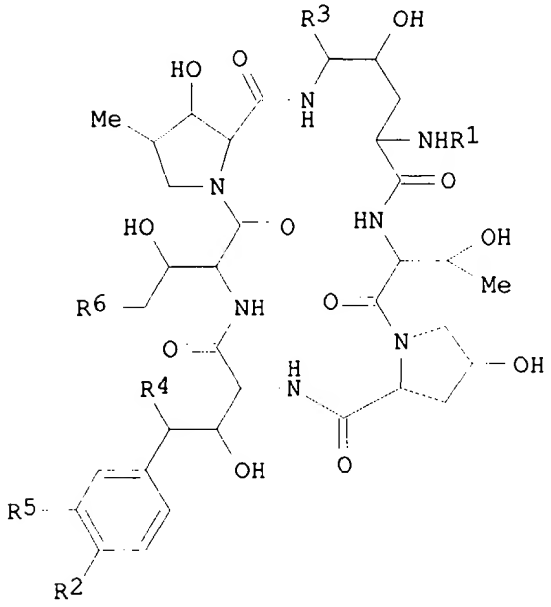

I

AB A cyclic lipopeptide acylase which can effectively remove acyl side chains from cyclic lipopeptides, e.g., FR901379 (I; R1=acyl; R2=OH,acyloxy; R3=H,OH;R4=H,OH; R5=H,hydroxysulfonyloxy; R6=H,carbamoyl), is prepared from Oidiodendron or Verticillium and used for the preparation of cyclic peptides II (R1-6 as in I). The enzyme exhibits a pH optimum 2-4, temperature optimum 25-45°, mol. weight 150 kDa, Vmax 4.2 U/mg-protein, and Km 1590 μM.

IC ICM C12N009-80
ICS C12N001-14; C07K005-12

CC 7-2 (Enzymes)
Section cross-reference(s): 10, 15

ST cyclic lipopeptide acylase Oidiodendron Verticillium; FR901379 deacylation acylase

IT Deacylation
(cyclic lipopeptide acylase of Oidiodendron or Verticillium for deacylation of cyclic lipopeptide FR901379)

IT Lipopeptides
RL: BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(cyclic; cyclic lipopeptide acylase of Oidiodendron or Verticillium for deacylation of cyclic lipopeptide FR901379)

IT Oidiodendron
(strain 30084; cyclic lipopeptide acylase of Oidiodendron or Verticillium for deacylation of cyclic lipopeptide FR901379)

IT Verticillium
(strain 30085; cyclic lipopeptide acylase of Oidiodendron or Verticillium for deacylation of cyclic lipopeptide FR901379)

IT Oidiodendron echinulatum
(strain IFO 31963; cyclic lipopeptide acylase of Oidiodendron or Verticillium for deacylation of cyclic lipopeptide FR901379)

IT Oidiodendron tenuissimum
(strains IFO 6798, IFO 9951, and IFO 31812; cyclic lipopeptide acylase of Oidiodendron or Verticillium for deacylation of cyclic lipopeptide FR901379)

IT 197393-86-5P, Cyclic lipopeptide acylase
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(cyclic lipopeptide acylase of Oidiodendron or Verticillium for deacylation of cyclic lipopeptide FR901379)

IT 54651-05-7, Echinocandin B 58814-86-1, Aculeacin A 138328-74-2, FR 901379
RL: BSU (Biological study, unclassified); RCT (Reactant); BIOL (Biological study); RACT (Reactant or reagent)
(deacylation of; cyclic lipopeptide acylase of Oidiodendron or Verticillium for deacylation of cyclic lipopeptide FR901379)

L33 *ANSWER 19 OF 27 MARPAT COPYRIGHT 2003 ACS on STN*
ACCESSION NUMBER: 127:304770 MARPAT
TITLE: Novel cyclic lipopeptide acylase of Streptomyces for deacylation of cyclic lipopeptides
INVENTOR(S): Ueda, Satoshi; Tanaka, Miho; Ezaki, Masami; Sakamoto, Kazutoshi; Hashimoto, Seiji; Oohata, Nobutaka; Tsuboi, Masaru; Yamashita, Michio
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan; Ueda, Satoshi; Tanaka, Miho; Ezaki, Masami; Sakamoto, Kazutoshi; Hashimoto, Seiji; Oohata, Nobutaka; Tsuboi, Masaru; Yamashita, Michio

SOURCE: PCT Int. Appl., 50 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9732975	A1	19970912	WO 1997-JP692	19970306
W: CA, CN, JP, KR, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
JP 3128247	B2	20010129	JP 1997-531651	19970303
CA 2248348	AA	19970912	CA 1997-2248348	19970306
EP 885957	A1	19981223	EP 1997-905455	19970306
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE, FI				
CN 1218507	A	19990602	CN 1997-194475	19970306
JP 3123078	B2	20010109	JP 1997-511848	19970306
US 6207434	B1	20010327	US 1998-142045	19980903
US 6537789	B1	20030325	US 2000-656420	20000906
US 6573084	B1	20030603	US 2000-656417	20000906
PRIORITY APPLN. INFO.:			JP 1996-51386	19960308
			JP 1996-194207	19960724
			JP 1996-49202	19960306
			WO 1997-JP629	19970303
			WO 1997-JP692	19970306
			US 1998-142045	19980903

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** STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT **

AB A novel cyclic lipopeptide acylase was isolated from Streptomyces anulatus and used for deacylation of FR901379 (I; R1=acyl; R2=OH, acyloxy; R3,R4=H,OH; R5=H,hydroxysulfonyloxy; R6=H,carbamoyl) to obtain II (R2-6 as in I). The enzyme exhibits a pH optimum 8-9, temperature optimum 50°, and mol. weight 61 kDa (large peptide) and 19 kDa (small) by SDS-PAGE. The enzyme is active on FR901379, Echinoeandin B, and Aculeacin A; inactive on FR901469.

IC ICM C12N009-80

CC 7-2 (Enzymes)
Section cross-reference(s): 10, 34

ST Streptomyces cyclic lipopeptide acylase; FR901379 deacylation cyclic lipopeptide acylase

IT Lipopeptides
RL: RCT (Reactant); RACT (Reactant or reagent)
(cyclic; deacylation of; novel cyclic lipopeptide acylase of Streptomyces for deacylation of cyclic lipopeptides)

IT Streptomyces anulatus
(strain Number 4811; novel cyclic lipopeptide acylase of Streptomyces for deacylation of cyclic lipopeptides)

IT Streptomyces
(strain Number 6907; novel cyclic lipopeptide acylase of Streptomyces for deacylation of cyclic lipopeptides)

IT Streptomyces anulatus
(strain Number 8703; novel cyclic lipopeptide acylase of Streptomyces for deacylation of cyclic lipopeptides)
IT 138328-74-2, FR 901379
RL: RCT (Reactant); RACT (Reactant or reagent)
(deacylation of; novel cyclic lipopeptide acylase of Streptomyces for deacylation of cyclic lipopeptides)
IT 197393-86-5P, Cyclic lipopeptide acylase
RL: BAC (Biological activity or effector, except adverse); BPN (Biosynthetic preparation); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(novel cyclic lipopeptide acylase of Streptomyces for deacylation of cyclic lipopeptides)

L33 ANSWER 20 OF 27 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 125:222461 MARPAT
TITLE: Preparation of novel antifungal cyclohexapeptides
INVENTOR(S): Bouffard, Frances A.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: PCT Int. Appl., 85 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9622784	A1	19960801	WO 1996-US921	19960122
W: AL, AM, AU, AZ, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TR, TT, UA, US, UZ, VN, AZ, BY, KG, KZ, RU				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2211138	AA	19960801	CA 1996-2211138	19960122
AU 9651681	A1	19960814	AU 1996-51681	19960122
AU 691743	B2	19980521		
EP 805685	A1	19971112	EP 1996-908446	19960122
EP 805685	B1	20010926		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, PT, IE				
JP 10505100	T2	19980519	JP 1996-522987	19960122
JP 2966936	B2	19991025		
AT 206054	E	20011015	AT 1996-908446	19960122
ES 2162039	T3	20011216	ES 1996-908446	19960122
US 5854213	A	19981229	US 1997-870744	19970606
PRIORITY APPLN. INFO.:			US 1995-378687	19950126
			WO 1996-US921	19960122

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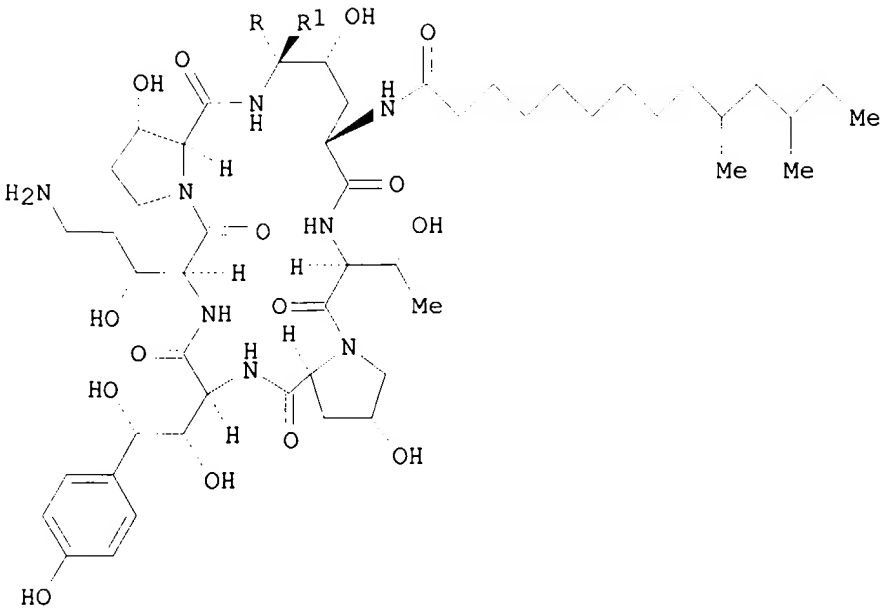

I

AB Novel carba cyclohexapeptide compds., e.g. (I.2HCl; R = CH2NH2, R1 = H) (I-A), which are useful as antifungal agents, in particular for the treatment of Pneumocystis carinii infections in immuno-compromised patients susceptible to infection, such as those suffering form AIDS, are prepared Thus, 0.4 mL CF3CO2H was added to a solution of 22.9 g I.HCl (R = OH, R1 = H) and 47.9 g H2NCH2CH2SH.HCl in 100 mL DMF and heated at 60° for 4 h to give a mixture of 6.5 g nor-thioether I.2CF3CO2H (R = H2NCH2CH2S, R1 = H) and 6.8 g epi-thioether I.2CF3CO2H (R = H, R1 = H2NCH2CH2S). The epi-thioether (6.5 g) was oxidized with 3.1 OXONE in MeCN/H2O at 25° for 15 min to give the crude sulfone I.2CF3CO2H (R = H, R1 = H2NCH2CH2SO2) (73% purity), which was stirred with 0.5 M LiCN in DMF for 15 min to give 21% nor-nitrile I.2CF3CO2H (R = cyano, R1 = H) and 36% epi-nitrile I.2CF3CO2H (R = H, R1 = cyano). The nor-nitrile (283 mg) was reduced by 91.2 mg NaBH4 in the presence of 115 mg COCl2.6H2O in MeOH, treated with 2 N aqueous CF3CO2H, and then purified by a column of Bio-Rad AG2-X8 (Cl-) resin to give I-A. I-A in vitro showed min. fungicidal concentration of <0.06, <0.06, and 0.25 μg/mL against Candida albicans (MY1055), C. tropicalis (MY1012), and C. glabrata (MY1381), resp., and in vivo reduced P. carinii cysts in 5 rats by at least 90% when dosed at 0.02 mg/kg with all rats surviving.

IC ICM A61K038-00

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1

ST antifungal cyclohexapeptide prepn; Pneumocystis carinii infection AIDS

IT Acquired immune deficiency syndrome
(Pneumocystis carinii infection; preparation of antifungal cyclohexapeptides)

IT Pneumocystis carinii
(infection in AIDS patients; preparation of antifungal

cyclohexapeptides)

IT Aspergillus
Candida albicans
Candida glabrata
Candida tropicalis
Fungicides and Fungistats
(preparation of antifungal cyclohexapeptides)

IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclohexa-, preparation of antifungal cyclohexapeptides)

IT 181359-13-7P 181492-34-2P
RL: BPN (Biosynthetic preparation); PUR (Purification or recovery); RCT (Reactant); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(deacylation product of N-(dimethyltetradecanoyl)cyclohexapeptide derivative with Pseudomonas acidovorans; preparation of antifungal cyclohexapeptides)

IT 181358-43-0P 181358-46-3P 181358-49-6P 181358-51-0P
181358-54-3P 181358-57-6P 181358-59-8P 181358-61-2P
181358-64-5P 181358-66-7P 181358-67-8P 181358-69-0P
181358-70-3P 181358-73-6P 181358-74-7P 181358-75-8P
181358-76-9P 181358-77-0P 181358-79-2P 181358-84-9P
181492-27-3P 181492-28-4P 181492-29-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of antifungal cyclohexapeptides)

IT 74-88-4, Iodomethane, reactions 110-53-2, n-Pentyl bromide
156-57-0, 2-Aminoethanethiol hydrochloride 771-61-9, Pentafluorophenol 1184-90-3, Aminoiminomethanesulfonic acid
2408-36-8, Lithium cyanide 5419-55-6, Triisopropyl borate
13795-24-9 16748-79-1 29558-77-8, 4-(4-Bromophenyl)phenol
53844-02-3 106359-65-3, 6-Octyloxy-2-naphthoic acid 135575-42-7, Pneumocandin B0 150167-55-8
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of antifungal cyclohexapeptides)

IT 63619-51-2P 150167-64-9P 150336-33-7P 158937-25-8P
160430-94-4P 161216-99-5P 179463-15-1P 179463-16-2P
179463-18-4P 181359-02-4P 181359-09-1P 181359-11-5P
181359-16-0P 181359-19-3P 181359-21-7P 181359-24-0P
181359-27-3P 181359-29-5P 181359-32-0P 181492-30-8P
181492-31-9P 181492-32-0P 181492-33-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of antifungal cyclohexapeptides)

L33 ANSWER 21 OF 27 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 125:143316 MARPAT
TITLE: Aza cyclohexapeptide compounds
INVENTOR(S): Balkovec, James M.; Bouffard, Frances A.; Dropinski, James F.
PATENT ASSIGNEE(S): Merck and Co., Inc., USA
SOURCE: PCT Int. Appl., 86 pp.
CODEN: PIXXD2

DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9613272	A1	19960509	WO 1995-US14026	19951027
W: AL, AM, AU, BB, BG, BR, BY, CA, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, US, UZ				
RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5516756	A	19960514	US 1994-333574	19941031
CA 2202920	AA	19960509	CA 1995-2202920	19951027
AU 9540164	A1	19960523	AU 1995-40164	19951027
AU 691998	B2	19980528		
EP 789579	A1	19970820	EP 1995-938980	19951027
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
JP 10508026	T2	19980804	JP 1995-514806	19951027

PRIORITY APPLN. INFO.: US 1994-333574 19941031
WO 1995-US14026 19951027

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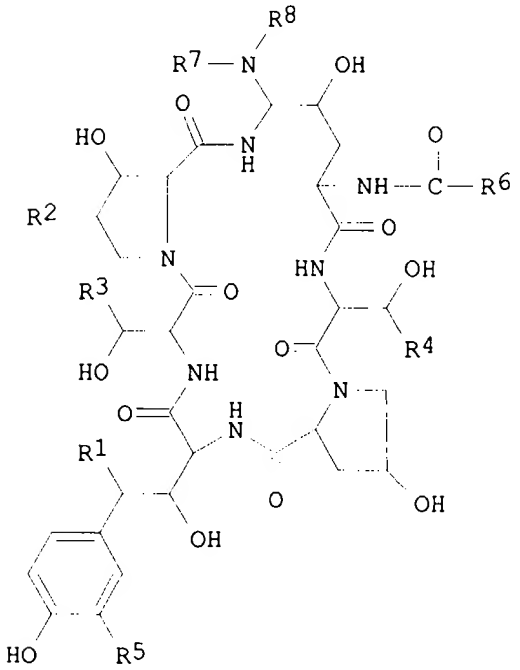

I

AB Aza cyclohexapeptides I [R1 = H, OH; R2 = H, Me, OH; R3 = H, Me, CH2CONH2, CH2CN, CH2CH2NH2, etc.; R4 = H, Me; R5 = H, OH, OSO3H; R6

= C9-H21 alkyl or alkenyl, C1-C10 alkoxyphenyl or -naphthyl, etc.; R7 = D- or L-H2NCH2CH(NH2)CO, Me3N+CH2CH2, H2NC(:NH)NHCH2CH2, etc.; R8 = H, C1-C4 alkyl] were prepared for use as antifungal agents and for the treatment of Pneumocystis carinii infections. Compns. containing the compds. of the invention are also disclosed. Thus, I [R1 = OH, R2 = R5 = R8 = H, R3 = CH2CH2NH2, R4 = Me, R6 = 9,11-dimethyltridecyl, R7 = L-H2NCH2CH(NH2)CO] (stereochem. not shown, isolated as the trifluoroacetate) was prepared by coupling I (R7 = H) with N,N-di-CBZ-L-2,3-diaminopropionic acid, followed by hydrogenolysis.

IC ICM A61K038-12
ICS C07K007-52

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 10

ST aza cyclohexapeptide prepn fungicide; pneumonia treatment aza cyclohexapeptide

IT Fungicides and Fungistats
Pneumocystis carinii
(preparation of cyclohexapeptides as antifungal agents and for treatment of Pneumocystis carinii infections.)

IT Peptides, preparation
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of cyclohexapeptides as antifungal agents and for treatment of Pneumocystis carinii infections.)

IT 179171-81-4P 179171-88-1P
RL: BPN (Biosynthetic preparation); RCT (Reactant); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of cyclohexapeptides as antifungal agents and for treatment of Pneumocystis carinii infections.)

IT 179171-82-5P
RL: BPN (Biosynthetic preparation); RCT (Reactant); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent)
(preparation of cyclohexapeptides as antifungal agents and for treatment of Pneumocystis carinii infections.)

IT 179171-84-7P 179171-90-5P
RL: BPN (Biosynthetic preparation); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of cyclohexapeptides as antifungal agents and for treatment of Pneumocystis carinii infections.)

IT 75-21-8, Oxirane, reactions 110-53-2, Pentyl bromide 110-85-0, Piperazine, reactions 111-40-0 111-83-1, Octyl bromide 112-24-3 156-57-0, 2-Aminoethanethiol hydrochloride 619-58-9, 4-Iodobenzoic acid 693-67-4, 1-Bromoundecane 771-61-9, Pentafluorophenol 1184-90-3, Formamidine sulfonic acid 1482-97-9, L-α,β-Diaminopropionic acid hydrochloride 29558-77-8 31252-42-3 40501-41-5 58574-03-1, 4-(4-Hydroxyphenyl)benzoic acid 150167-55-8 179171-77-8 179463-17-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(preparation of cyclohexapeptides as antifungal agents and for treatment of Pneumocystis carinii infections.)

IT 10256-43-6P 59748-18-4P 63619-51-2P 65621-26-3P 82394-26-1P 157136-82-8P 158937-25-8P 158937-79-2P 158937-98-5P 160430-94-4P 160430-98-8P 161216-99-5P 179171-68-7P 179171-70-1P 179171-92-7P 179171-93-8P 179171-94-9P 179171-95-0P 179171-96-1P 179171-97-2P 179171-98-3P 179463-15-1P 179463-16-2P 179463-18-4P 179463-20-8P

RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation of cyclohexapeptides as antifungal agents and for treatment of Pneumocystis carinii infections.)

IT 150167-64-9P 150336-33-7P 158938-08-0P 160430-95-5P
160430-96-6P 160430-97-7P 179171-69-8P 179171-71-2P
179171-72-3P 179171-73-4P 179171-74-5P 179171-75-6P
179171-76-7P 179171-78-9P 179171-79-0P 179171-83-6P
179171-85-8P 179171-86-9P 179171-89-2P 179463-21-9P
179601-12-8P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of cyclohexapeptides as antifungal agents and for treatment of Pneumocystis carinii infections.)

L33 ANSWER 22 OF 27 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 123:228903 MARPAT
TITLE: Preparation of cyclic peptide compounds as β-1,3-glucan synthase inhibitors and antimicrobial agents
INVENTOR(S): Ohki, Hidenori; Tomishima, Masaki; Yamada, Akira; Takasugi, Hisashi
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE: Can. Pat. Appl., 85 pp.
CODEN: CPXXEB
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2123921	AA	19941118	CA 1994-2123921	19940517
AU 9461994	A1	19941124	AU 1994-61994	19940510
AU 681119	B2	19970821		
IL 109615	A1	20001206	IL 1994-109615	19940510
EP 644199	A1	19950322	EP 1994-107406	19940512
EP 644199	B1	20000719		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
AT 194846	E	20000815	AT 1994-107406	19940512
ES 2148254	T3	20001016	ES 1994-107406	19940512
CN 1100104	A	19950315	CN 1994-105193	19940516
CN 1057306	B	20001011		
ZA 9403356	A	19950328	ZA 1994-3356	19940516
HU 68385	A2	19950628	HU 1994-1515	19940516
US 5569646	A	19961029	US 1994-242854	19940516
RU 2164230	C2	20010320	RU 1994-16354	19940516
JP 06340693	A2	19941213	JP 1994-126977	19940517
US 5693750	A	19971202	US 1996-675212	19960703
PRIORITY APPLN. INFO.:			GB 1993-10091	19930517
			GB 1993-25269	19931210
			US 1994-242854	19940516

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Cyclic peptide compds. [I; R1 = H; R2 = acyl; R3 = OH, acyloxy; R4 =HO, OSO3H; R5 = H or a lower alkyl group which is optionally substituted with a HO, acyl, di(lower)alkylamino or cyclic amino group; R6 = H, OH, or acyl-lower alkylthio] and pharmaceutically acceptable salts thereof, useful as fungicides for the treatment of Pneumocystis carinii infection, are prepared Thus, 0.285 g NaBH3CN was added to a solution of 1 g I (R1 = R3 = R6 = OH, R2 = Q, R4 = NaO3SO, R5 = H) in CF3CO2H containing mol. sieves 4A and the resulting mixture was stirred at ambient temperature for 1 h to give, after chromatog. by an ion-exchange column on DOWEX 50WX4 (Na+-type) and HPLC using a C18μ Bondpak resin, column chromatog. on ODS (YMC-gel ODS-AMS-50), and lyophilization, 318 mg I (R1 = R5 = H, R2 = Q, R3 = R6 = OH, R4 = NaO3SO) and 263 mg I (R1 = R5 = R6 = H, R2 = Q, R6 = OH, R4 = NaO3SO). I (R1 = R5 = H, R2 = Q1, R3 = R6 = OH, R4 = NaO3SO) showed IC50 of 0.05 μg/mL against Candida albicans YU-1200.

IC ICM C07K007-56
ICS C07K001-00; A61K037-02

CC 34-3 (Amino Acids, Peptides, and Proteins)

ST cyclic peptide prepn fungicide; beta glucan synthase inhibitor cyclic peptide

IT Pneumocystis carinii
(preparation of cyclic peptide compds. for treatment of Pneumocystis carinii infection)

IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclo-, preparation of cyclic peptide compds. as β-1,3-glucan synthase inhibitors and fungicides)

IT 20276-55-5P, 1-Methylenepiperidinium chloride 59748-15-1P, 4-(4-Pentyloxyphenyl)benzoic acid 69367-31-3P, 4-(4-Nonyloxyphenyl)benzoic acid 106359-64-2P, 6-Heptyloxy-2-naphthoic acid 152490-93-2P 165727-73-1P 165727-74-2P 165727-82-2P 165727-83-3P 167090-66-6P 167090-67-7P 167090-68-8P 167090-69-9P 167090-70-2P 167090-74-6P, 6-(4-Methylpentyloxy)-2-naphthoic acid 168110-45-0P 168110-46-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(intermediate for preparation of fungicidal cyclic peptide compds.)

IT 167090-46-2P 167090-47-3P 167090-48-4P 167090-49-5P 167090-50-8P 167090-51-9P 167090-52-0P 167090-53-1P 167090-54-2P 167090-55-3P 167090-56-4P 167090-57-5P 167090-58-6P 167090-59-7P 167090-60-0P 167090-61-1P 167090-62-2P 167090-63-3P 167090-64-4P 167090-65-5P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of cyclic peptide compds. as β-1,3-glucan synthase inhibitors and fungicides)

IT 9037-30-3, β-1,3-Glucan synthase
RL: BSU (Biological study, unclassified); MSC (Miscellaneous); BIOL (Biological study)
(preparation of cyclic peptide compds. as β-1,3-glucan synthase

inhibitors and fungicides)

IT 68-11-1, Mercaptoacetic acid, reactions 298-12-4, Glyoxylic acid 629-04-9, Heptyl bromide 1931-98-2 6066-82-6, N-Hydroxysuccinimide 16712-64-4, 6-Hydroxy-2-naphthoic acid 138328-74-2 141518-38-9 141518-53-8 144371-85-7 152868-85-4 152868-93-4 152868-94-5 165727-69-5 165727-74-2 167090-72-4 167090-73-5 168110-44-9 168110-47-2 168110-48-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction in preparation of fungicidal cyclic peptide compds.)

L33 ANSWER 23 OF 27 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 122:82078 MARPAT
TITLE: Cyclic peptide antifungal agents and process for preparation thereof
INVENTOR(S): Burkhardt, Frederick Joseph; Debono, Manuel; Nissen, Jeffrey Scott; Turner, William Wilson, Jr.
PATENT ASSIGNEE(S): Lilly, Eli, and Co., USA
SOURCE: Eur. Pat. Appl., 56 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 561639	A1	19930922	EP 1993-302064	19930318
EP 561639	B1	20020515		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, NL, PT, SE				
CA 2091663	AA	19930920	CA 1993-2091663	19930315
ZA 9301830	A	19940915	ZA 1993-1830	19930315
IL 105048	A1	20010614	IL 1993-105048	19930315
NZ 299314	A	20010928	NZ 1993-299314	19930315
CZ 288974	B6	20011017	CZ 1993-416	19930315
IL 122315	A1	20020310	IL 1993-122315	19930315
NZ 512085	A	20030829	NZ 1993-512085	19930315
NO 9300948	A	19930920	NO 1993-948	19930316
BR 9301232	A	19930921	BR 1993-1232	19930318
HU 63637	A2	19930928	HU 1993-785	19930318
CN 1080926	A	19940119	CN 1993-103587	19930318
CN 1036715	B	19971217		
JP 06056892	A2	19940301	JP 1993-58529	19930318
RU 2129562	C1	19990427	RU 1993-4787	19930318
AT 217635	E	20020615	AT 1993-302064	19930318
JP 2002226500	A2	20020814	JP 2002-3969	19930318
ES 2174843	T3	20021116	ES 1993-302064	19930318
AU 9335341	A1	19930923	AU 1993-35341	19930319
AU 9665529	A1	19961205	AU 1996-65529	19960909
AU 689391	B2	19980326		
PRIORITY APPLN. INFO.:			US 1992-854117	19920319
			US 1992-992390	19921216
			IL 1993-105048	19930315
			JP 1993-58529	19930318

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* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Title compds. (I; R, R11 = independently H, OH; R1 = H, OH, OSO3H; R2 = substituted PhCO, biphenylyl, naphthoyl, etc.; R7 = R1, phosphonooxy; R8 = H, Me, H2NCOCH2; R9, R10 = Me, H), were prepared Thus, I (R = R7 = R11 = OH, R1 = H, R2 = Q1, R8 = R9 = R10 = Me), prepared by enzymic deacylation and then reacylation of echinocandin B, showed ED50 = 0.84 mg/mL for controlling systemic fungal infections in mice. Several I were effective against Pneumocystis carinii in immunosuppressed rats. I in general exhibit oral bioavailability.

IC ICM C07K007-56
ICS A61K037-02

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1

ST peptide cyclic prepn medical fungicide; echinocandin analog prepn medical fungicide

IT Fungicides and Fungistats
(cyclic peptide derivs)

IT Peptides, preparation
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(cyclo-, preparation of, as medical fungicides)

IT 79411-15-7
RL: RCT (Reactant); RACT (Reactant or reagent)
(acylation of, in preparation of medical fungicide)

IT 5731-15-7P 25739-23-5P 41424-11-7P 42497-80-3P 52364-71-3P
52709-87-2P 59748-14-0P 59748-15-1P 59748-16-2P 75867-41-3P
82175-72-2P 89752-76-1P 117802-43-4P 117802-44-5P
118788-02-6P 140714-91-6P 144493-15-2P 144540-61-4P
158936-92-6P 158936-93-7P 158936-94-8P 158936-95-9P
158936-96-0P 158936-97-1P 158936-98-2P 158936-99-3P
158937-00-9P 158937-01-0P 158937-02-1P 158937-03-2P
158937-04-3P 158937-05-4P 158937-06-5P 158937-07-6P
158937-08-7P 158937-09-8P 158937-10-1P 158937-11-2P
158937-12-3P 158937-13-4P 158937-14-5P 158937-15-6P
158937-16-7P 158937-17-8P 158937-18-9P 158937-19-0P
158937-20-3P 158937-21-4P 158937-22-5P 158937-23-6P
158937-24-7P 158937-25-8P 158937-26-9P 158937-27-0P
158937-28-1P 158937-29-2P 158937-30-5P 158937-31-6P
158937-32-7P 158937-33-8P 158937-34-9P 158937-35-0P
158937-36-1P 158937-37-2P 158937-38-3P 158937-39-4P
158937-40-7P 158937-41-8P 158937-42-9P 158937-43-0P
158937-44-1P 158937-45-2P 158937-46-3P 158937-47-4P
158937-48-5P 158937-49-6P 158937-50-9P 158937-51-0P
158937-52-1P 158937-53-2P 158937-54-3P 158937-55-4P
158937-56-5P 158937-57-6P 158937-58-7P 158937-59-8P
158937-60-1P 158937-61-2P 158937-62-3P 158937-63-4P
158937-64-5P 158937-65-6P 158937-66-7P 158937-67-8P
158937-68-9P 158937-69-0P 158937-70-3P 158937-71-4P
158937-72-5P 158937-73-6P 158937-86-1P 158937-87-2P
158937-88-3P 158937-89-4P 158937-90-7P 158937-91-8P
158937-92-9P 158937-93-0P 158937-94-1P 158937-95-2P
158937-96-3P 158937-97-4P 158937-98-5P 158937-99-6P

158938-00-2P 158938-01-3P 158938-02-4P 158938-03-5P
158938-04-6P 158938-05-7P 158938-06-8P 158938-07-9P
158938-08-0P 158938-09-1P 158938-10-4P 158938-11-5P
158938-12-6P 158938-13-7P 158938-14-8P 158938-15-9P
158938-16-0P 158938-17-1P 160442-19-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as intermediate for cyclic peptide deriv medical fungicide)

IT 158935-94-5P 158935-95-6P 158935-96-7P 158935-97-8P
158935-98-9P 158935-99-0P 158936-00-6P 158936-01-7P
158936-02-8P 158936-03-9P 158936-04-0P 158936-05-1P
158936-06-2P 158936-07-3P 158936-08-4P 158936-09-5P
158936-10-8P 158936-11-9P 158936-12-0P 158936-13-1P
158936-14-2P 158936-15-3P 158936-16-4P 158936-17-5P
158936-18-6P 158936-19-7P 158936-20-0P 158936-21-1P
158936-22-2P 158936-23-3P 158936-24-4P 158936-25-5P
158936-26-6P 158936-27-7P 158936-28-8P 158936-29-9P
158936-30-2P 158936-31-3P 158936-32-4P 158936-33-5P
158936-34-6P 158936-35-7P 158936-36-8P 158936-37-9P
158936-38-0P 158936-39-1P 158936-40-4P 158936-41-5P
158936-42-6P 158936-43-7P 158936-44-8P 158936-45-9P
158936-46-0P 158936-47-1P 158936-48-2P 158936-49-3P
158936-50-6P 158936-51-7P 158936-52-8P 158936-53-9P
158936-54-0P 158936-55-1P 158936-56-2P 158936-57-3P
158936-58-4P 158936-59-5P 158936-60-8P 158936-61-9P
158936-62-0P 158936-63-1P 158936-64-2P 158936-65-3P
158936-66-4P 158936-67-5P 158936-68-6P 158936-69-7P
158936-70-0P 158936-71-1P 158936-72-2P 158936-73-3P
158936-74-4P 158936-75-5P 158936-76-6P 158936-77-7P
158936-78-8P 158936-79-9P 158936-80-2P 158936-81-3P
158936-82-4P 158936-83-5P 158936-84-6P 158936-85-7P
158936-86-8P 158936-87-9P 158936-88-0P 158936-89-1P
158936-90-4P 158936-91-5P 159000-67-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as medical fungicide)

IT 107-08-4, 1-Iodopropane 107-82-4 110-53-2, 1-Bromopentane 111-66-0, 1-Octene 536-74-3 540-38-5, 4-Iodophenol 542-69-8, 1-Iodobutane 619-44-3, Methyl 4-iodobenzoate 629-05-0, 1-Octyne 638-45-9, 1-Iodohexane 693-02-7, 1-Hexyne 764-93-2, 1-Decyne 1066-54-2 1647-26-3, 1-Bromo-2-cyclohexylethane 2038-91-7 2346-07-8 2527-99-3, Methyl 5-bromofuran-2-carboxylate 3034-86-4 6661-54-7 13295-53-9, Cyclobutylmethyl tosylate 21856-53-1, Cyclopentylmethyl tosylate 29558-77-8 60834-63-1 62124-28-1 63619-51-2 63619-63-6 63619-64-7 108366-80-9 141430-54-8 158407-15-9 158937-74-7 158937-75-8 158937-76-9 158937-77-0 158937-78-1 158937-79-2 158937-80-5 158937-81-6 158937-82-7 158937-83-8 158937-84-9 158937-85-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in preparation of cyclic peptide deriv medical fungicide)

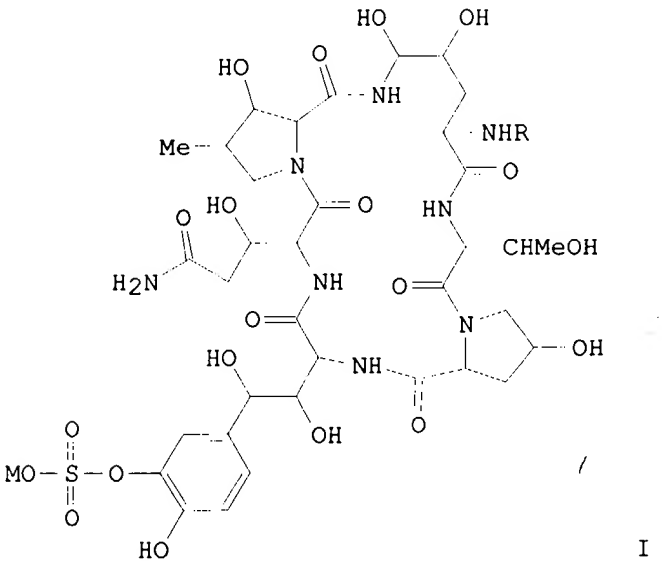
IT 79404-91-4, Cilofungin
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in preparation of medical fungicide)

L33 ANSWER 24 OF 27 MARPAT COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 120:164908 MARPAT
TITLE: Preparation of cyclic peptide derivatives as antibacterial agents
INVENTOR(S): Oki, Hidetoku; Kawabata, Koji; Itane, Kazuo
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 21 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 05202096	A2	19930810	JP 1992-291149	19921029
PRIORITY APPLN. INFO.:			GB 1991-23046	19911030

GI



I

AB N-acylcyclopeptides [I; M = H; R = C9-10 (1 or 2 halo-substituted)alkoxy-benzoyl, (un)protected carboxybenzoyl, carboxy-higher alkoxy-benzoyl, lower alkoxyphenyl-benzoyl, hydroxy-higher alkoxyphenyl-benzoyl, lower alkenyloxyphenyl-benzoyl, C7 alkoxy-naphthoyl, (un)substituted aroylamino-lower alkanoyl, (un)substituted indolyl- or pyrazolyl-lower alkanoyl, steroid-containing lower alkanoyl] or their salts are prepared Thus, 0.393 g 4-dimethylaminopyridine was added to a solution of 2.8 g 6-heptyloxy-2-naphthoic acid N-hydroxysuccinimide ester (preparation given) and I (M = Na, R = H) in DMF and the solution was stirred at room temperature for 12 h to give, after ion column chromatog. using Dowex-50WX4 and column chromatog. using ODS YMC-gel (ODS-AM S-50) (Yamamura Kagaku Kenkyusho Inc., Ltd.), 1.94 g I (M = Na, R = 6-heptyloxy-2-naphthoyl) (II). II showed min. inhibitory concentration of 0.1 μg/mL against Candida albicans FP579. A total of 21 I (M = Na) were prepared

IC ICM C07K007-56
ICS A61K037-02; C07K001-02
ICI C07K099-00
CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1
ST cyclic peptide prepn antibacterial; acylcyclopeptide prepn antibacterial
IT Bactericides, Disinfectants, and Antiseptics
(N-acylcyclopeptides)
IT Peptides, preparation
RL: SPN (Synthetic preparation); PREP (Preparation)
(cyclo-, acyl derivs., preparation of, as antibacterial agents)
IT 141518-06-1
RL: RCT (Reactant); RACT (Reactant or reagent)
(acylation of, in preparation of antibacterial N-acylcyclopeptide)
IT 152868-85-4P 152868-86-5P 152868-87-6P 152868-88-7P
152868-89-8P 152868-90-1P 152868-91-2P 152868-92-3P
152868-93-4P 152868-94-5P 152868-95-6P 152868-96-7P
152868-97-8P 152868-98-9P 152868-99-0P 152869-00-6P
152869-01-7P 152869-02-8P 152869-03-9P 152869-04-0P
152869-05-1P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(preparation of, as antibacterial agent)
IT 74-88-4P, Methyl iodide, preparation 553-90-2P, Dimethyl oxalate
13423-56-8P, 4-Octyloxycarbonylbenzoyl chloride 37062-63-8P
59748-16-2P 62443-22-5P, 4-(3,7-Dimethyloctyloxy)benzoic acid
73881-10-4P, (E)-2-Hexen-1-yl bromide 104211-94-1P 106359-64-2P,
6-Heptyloxy-2-naphthoic acid 123598-57-2P 152490-93-2P,
6-Heptyloxy-2-naphthoic acid N-hydroxysuccinimide ester
152490-94-3P 152490-95-4P 152490-96-5P, Methyl
3-(4-octyloxybenzoyl)pyruvate 152490-97-6P, Methyl
5-(4-octyloxybenzoyl)pyrazole-3-carboxylate 152490-98-7P,
1-Methyl-5-decyloxyindole-2-carboxylic acid 152490-99-8P,
5-(4-Octyloxybenzoyl)pyrazole-3-carboxylic acid 152491-00-4P
152491-01-5P, 4-(3,7-Dimethyloctyloxy)-3-fluorobenzoic acid
152491-02-6P, 4-(3,7-Dimethyloctyloxy)-2,3,5,6-tetrafluorobenzoic acid 152491-03-7P 152491-04-8P 152491-05-9P 152491-06-0P
152491-07-1P 152491-08-2P 152491-09-3P, 5-Octyloxyindole-2-carboxylic acid 152491-10-6P, 5-Decyloxyindole-2-carboxylic acid
152491-11-7P 152491-12-8P 152491-13-9P 152491-14-0P
152491-15-1P 152491-16-2P 152491-17-3P 152491-18-4P
152491-19-5P 152491-20-8P 152491-21-9P 152491-22-0P
152491-23-1P 152491-24-2P 152491-25-3P 152491-26-4P
152491-27-5P 152491-28-6P 152491-29-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as intermediate for antibacterial N-acylcyclopeptide)
IT 56-41-7, L-Alanine, reactions 100-20-9, Terephthaloyl dichloride
106-21-8, 3,7-Dimethyloctanol 111-87-5, n-Octanol, reactions
455-86-7, 3,4-Difluorobenzoic acid 629-04-9, Heptyl bromide
928-95-0, (E)-2-Hexen-1-ol 6066-82-6, N-Hydroxysuccinimide
16712-64-4, 6-Hydroxy-2-naphthoic acid 152491-17-3
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in preparation of antibacterial N-acylcyclopeptide)

L33 ANSWER 25 OF 27 MARPAT COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 118:213544 MARPAT
TITLE: Pharmaceutical composition against Pneumocystis carinii
INVENTOR(S): Furuta, Takahisa; Iwamoto, Toshiro; Fujie, Akihiko; Nitta, Kumiko; Tsurumi, Yasuhisa; Shigematsu, Nobuharu; Kasahara, Chiyoshi; Hino, Motohiro; Okuhara, Masakuni
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE: Eur. Pat. Appl., 69 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 486011	A2	19920520	EP 1991-119421	19911114
EP 486011	A3	19920715		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
JP 05000966	A2	19930108	JP 1991-354117	19911115
US 1638	H1	19970304	US 1994-311434	19940926
PRIORITY APPLN. INFO.:			US 1990-614125	19901116
			GB 1990-27152	19901214
			GB 1991-1552	19910124
			GB 1991-6822	19910402
			US 1990-610759	19901108
			US 1991-791926	19911115

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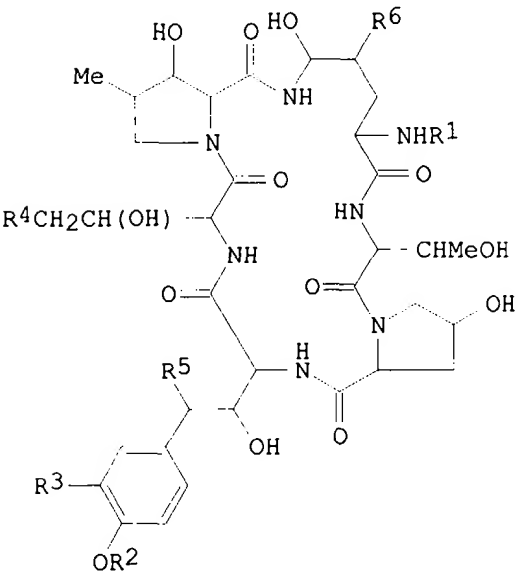

I

AB FR 901379 derivs. I (R1, R2 = H, acyl; R3 = H, OH, O3SOH; R4 = H, carbamoyl; R5, R6 = H, OH) were prepared Thus, FR 901379 [I, R1 = CO(CH2)14Me, R2 = H, R3 = O3SOH, R4 = CONH2, R5, R6 = OH, II] was

isolated from a culture of Coleophoma sp. F-11899 and deacylated with Actinoplanes utahensis to give II (R1 = H). Acylation of II (R1 = H) with 2,4,5-Cl3C6H2O2CC6H4O(CH2)7Me-4 gave II [R1 = COC6H4O(CH2)7Me-4] which at 2 mg/day i.p. in rats showed significant inhibition of P. carinii pneumocysts.

IC ICM A61K037-02

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1

ST FR 901379 isolation derivatization; FR 131535 prepn Pneumocystis bactericide; antibiotic Coleophoma cyclic peptide

IT Antibiotics
Bactericides, Disinfectants, and Antiseptics
(FR 901379 derivs.)

IT Pneumocystis carinii
(infection by, FR 901379 derivs. in treatment of)

IT 355-80-6
RL: RCT (Reactant); RACT (Reactant or reagent)
(alkylation by, of pentafluorobenzoic acid)

IT 111-83-1, 1-Bromooctane
RL: RCT (Reactant); RACT (Reactant or reagent)
(alkylation by, of phenol derivs.)

IT 99-96-7, 4-Hydroxybenzoic acid, reactions 602-94-8 626-64-2, 4-Hydroxypyridine 16712-64-4, 6-Hydroxy-2-naphthoic acid
RL: RCT (Reactant); RACT (Reactant or reagent)
(alkylation of)

IT 106-21-8, 3,7-Dimethyl-1-octanol
RL: RCT (Reactant); RACT (Reactant or reagent)
(bromination of)

IT 1818-07-1, Octyl phenyl ether
RL: RCT (Reactant); RACT (Reactant or reagent)
(chlorosulfonylation of)

IT 2488-14-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(ester hydrolysis of)

IT 95-95-4, 2,4,5-Trichlorophenol
RL: RCT (Reactant); RACT (Reactant or reagent)
(esterification by, of octyloxybenzoic acid)

IT 22818-40-2
RL: RCT (Reactant); RACT (Reactant or reagent)
(esterification of)

IT 144371-88-0P, FR 901379
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study); PREP (Preparation)
(isolation and bactericidal activity of, against Pneumocystis carinii)

IT 138328-74-2P
RL: RCT (Reactant); PREP (Preparation); RACT (Reactant or reagent)
(isolation and desulfonation of)

IT 138328-75-3P, FR 901381 138626-86-5P, FR 901382
RL: PREP (Preparation)
(isolation of)

IT 141518-06-1P, FR 133303
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and acylation of)

IT 3383-83-3P, 3,7-Dimethyl-1-bromooctane 4895-14-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);

RACT (Reactant or reagent)
(preparation and alkylation by, of phenol derivs.)
IT 38250-16-7P 57746-16-4P 76529-98-1P 76757-90-9P 141518-55-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);
RACT (Reactant or reagent)
(preparation and alkylation of)
IT 144371-85-7P 144371-87-9P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and bactericidal activity of)
IT 141537-51-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);
RACT (Reactant or reagent)
(preparation and chlorination of)
IT 141518-08-3P 141537-39-5P 144371-86-8P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);
RACT (Reactant or reagent)
(preparation and deblocking of)
IT 141537-14-6P 141537-17-9P 141537-36-2P 141537-37-3P
141537-38-4P 141537-40-8P 141537-41-9P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);
RACT (Reactant or reagent)
(preparation and ester hydrolysis of)
IT 2493-84-7P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);
RACT (Reactant or reagent)
(preparation and esterification of)
IT 141537-63-5P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);
RACT (Reactant or reagent)
(preparation and hydrazinolysis of)
IT 21095-40-9P 79404-93-6P 117739-44-3P 141537-16-8P
141537-19-1P 141537-20-4P 141537-21-5P 141537-22-6P
141537-23-7P 141537-24-8P 141537-52-2P 141537-70-4P
141537-71-5P 141537-72-6P 141537-73-7P 141537-74-8P
141537-75-9P 141537-76-0P 141537-77-1P 141537-78-2P
141537-79-3P 141537-80-6P 141537-81-7P 144313-05-3P
144313-06-4P 144313-07-5P 144313-08-6P 144313-09-7P
144313-10-0P 144313-11-1P 144313-12-2P 144313-13-3P
144313-14-4P 144313-15-5P 144313-16-6P 144313-17-7P
144313-18-8P 144313-19-9P 144313-20-2P 144313-21-3P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);
RACT (Reactant or reagent)
(preparation and reaction of, with FR 133303)
IT 141537-35-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);
RACT (Reactant or reagent)
(preparation and reaction of, with FR 138728)
IT 141537-15-7P 141537-18-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation);
RACT (Reactant or reagent)
(preparation and reaction of, with disuccinimidyl carbonate)
IT 24495-07-6P 29148-14-9P 53346-59-1P 59748-18-4P 67132-02-9P
79785-55-0P 99196-58-4P 106359-65-3P 106359-66-4P
110209-08-0P 122527-97-3P 141537-25-9P 141537-26-0P
141537-42-0P 141537-43-1P 141537-44-2P 141537-45-3P
141537-46-4P 141537-47-5P 141537-48-6P 141537-49-7P

141537-50-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with hydroxybenzotriazole)

IT 67698-68-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with hydroxyphthalimide)

IT 141537-64-6P 141537-65-7P 141537-66-8P 141537-67-9P
141537-68-0P 141537-69-1P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with hydroxysuccinimide)

IT 141518-13-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and reaction of, with pyridinethione)

IT 141537-34-0P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and thiolation of)

IT 3728-20-9P, D-Tyrosine methyl ester hydrochloride 4326-36-7P
57591-61-4P
RL: RCT (Reactant); SPN (Synthetic preparation); PREP (Preparation); RACT (Reactant or reagent)
(preparation and tert-butoxycarbonylation of)

IT 138328-76-4P, FR 133302 141518-09-4P 141518-10-7P 141518-11-8P
141518-12-9P 141518-15-2P 141518-16-3P 141518-17-4P
141518-18-5P 141518-19-6P 141518-20-9P 141518-21-0P
141518-22-1P 141518-23-2P 141518-24-3P 141518-25-4P
141518-26-5P 141518-27-6P 141518-28-7P 141518-29-8P
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141518-46-9P 141518-47-0P 141518-48-1P 141518-49-2P
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141518-54-9P 141537-12-4P 141537-13-5P 144313-04-2P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of)

IT 22118-09-8, 2-Bromoacetyl chloride 91868-79-0 144313-22-4
144313-23-5
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with FR 133303)

IT 24083-13-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(reduction of)

L33 ANSWER 26 OF 27 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 117:49262 MARPAT
TITLE: Preparation of cyclic peptide (echinocandin B) antibiotics
INVENTOR(S): Toshiro, Iwamoto; Akihiko, Fujie; Kumiko, Nitta; Yasuhisa, Tsurumi; Nobuharu, Shigematsu; Chiyoshi, Kasahara; Motohiro, Hino; Masakuni, Okuhara; Kazuo, Sakane; et al.
PATENT ASSIGNEE(S): Fujisawa Pharmaceutical Co., Ltd., Japan
SOURCE: Eur. Pat. Appl., 69 pp.

CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 462531	A2	19911227	EP 1991-109856	19910615
EP 462531	A3	19921104		
EP 462531	B1	19961002		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
FI 9102873	A	19911219	FI 1991-2873	19910614
IL 98506	A1	19960912	IL 1991-98506	19910614
EP 729974	A1	19960904	EP 1995-117638	19910615
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
AT 143671	E	19961015	AT 1991-109856	19910615
ES 2093658	T3	19970101	ES 1991-109856	19910615
CA 2044746	AA	19911219	CA 1991-2044746	19910617
CA 2044746	C	20010807		
NO 9102347	A	19911219	NO 1991-2347	19910617
AU 9178435	A1	19920116	AU 1991-78435	19910617
AU 651347	B2	19940721		
HU 58108	A2	19920128	HU 1991-2014	19910617
US 5376634	A	19941227	US 1991-715961	19910617
RU 2108342	C1	19980410	RU 1991-4895760	19910617
CN 1059729	A	19920325	CN 1991-104847	19910618
CN 1040541	B	19981104		
ZA 9104677	A	19920429	ZA 1991-4677	19910618
JP 04352799	A2	19921207	JP 1991-245284	19910618
JP 3307410	B2	20020724		
US 1638	H1	19970304	US 1994-311434	19940926
PRIORITY APPLN. INFO.:			GB 1990-13558	19900618
			GB 1990-23666	19901031
			GB 1991-1552	19910124
			US 1990-610759	19901108
			US 1990-614125	19901116
			GB 1990-27152	19901214
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			EP 1991-109856	19910615
			US 1991-791926	19911115

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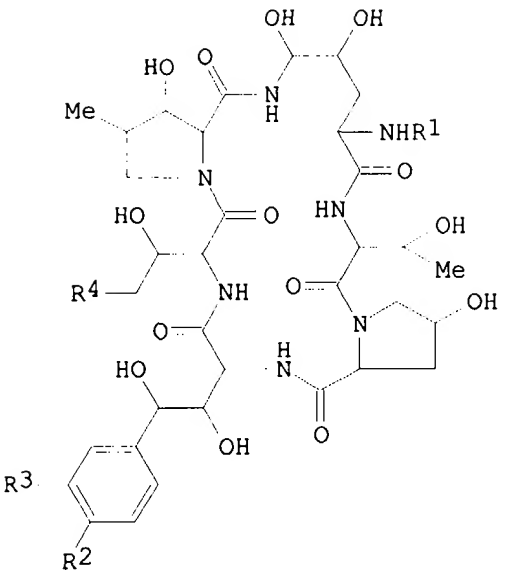

I

AB Title compds. (I; R1 = H, acyl; R2 = OH, acyloxy; R3 = H, HOSO2O; R4 = H, carbamoyl; with provisos that 1) R2 = acyloxy when R3 = H, and 2) R1 ≠ palmitoyl when R2 = OH, R3 = HOSO2O, R4 = carbamoyl), were prepared Thus, antibiotic FR901379 [I; R1 = Co(CH2)14Me, R2 = OH, R3 = OSO2Na, R4 = CONH2] (preparation given) was fermented with Actinoplanes utahensis IFO-13244 to give N-deacylation and the product was acylated with 2,4,5-trichlorophenyl 4-octyloxybenzoate (preparation given) to give I [R1 = COC6H4[O(CH2)7Me]-4, R2 = OH, R3 = OSO2ONa, R4 = CONH2] (II). II had IC50 = 0.31 (no units) against Candida albicans FP578. II at 500 mg/kg i.v. in mice was nontoxic.

IC ICM C07K007-56
ICS C12P021-04; C12N001-14

ICI C12N001-14, C12R001-645

CC 34-3 (Amino Acids, Peptides, and Proteins)
Section cross-reference(s): 1, 16

ST peptide cyclic prepn antibiotic; echinocandin B analog prepn antibiotic

IT Antibiotics
(cyclic polypeptides)

IT Fermentation
(of Coleophoma sp. F-11899, in preparation of cyclic polypeptide antibiotic)

IT Coleophoma
(strain F-11899, culture of, in preparation of cyclic polypeptide antibiotics)

IT Actinoplanes utahensis
(use of, in deacylation of cyclic peptide antibiotic)

IT Peptides, preparation
RL: SPN (Synthetic preparation); PREP (Preparation)
(cyclo-, echinocandin analogs, preparation of, as antibiotics)

IT 141518-06-1P 141518-08-3P 141518-09-4P 141518-10-7P
141518-11-8P 141518-12-9P 141518-13-0P 141518-14-1P
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141518-39-0P 141518-40-3P 141518-41-4P 141518-42-5P
141518-43-6P 141518-44-7P 141518-45-8P 141518-46-9P
141518-47-0P 141518-48-1P 141518-49-2P 141518-50-5P
141518-51-6P 141518-52-7P 141518-53-8P 141518-54-9P
141537-12-4P 141537-13-5P 144371-85-7P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation of, as antibiotic)

IT 2493-84-7P, 4-Octyloxybenzoic acid 3383-83-3P 3728-20-9P
4326-36-7P 4895-14-1P 21095-40-9P 24495-07-6P 29148-14-9P
38250-16-7P 53346-59-1P 57591-61-4P 57746-16-4P 59748-18-4P
67132-02-9P 67698-68-4P 76529-98-1P 76757-90-9P 79404-93-6P,
2,4,5-Trichlorophenyl 4-octyloxybenzoate 79785-55-0P 99196-58-4P
106359-65-3P 106359-66-4P 110209-08-0P 117739-44-3P
122527-97-3P 138328-74-2P 141518-55-0P 141537-14-6P
141537-15-7P 141537-16-8P 141537-17-9P 141537-18-0P
141537-19-1P 141537-20-4P 141537-21-5P 141537-22-6P
141537-23-7P 141537-24-8P 141537-25-9P 141537-26-0P
141537-27-1P 141537-28-2P 141537-29-3P 141537-30-6P
141537-31-7P 141537-32-8P 141537-33-9P 141537-34-0P
141537-35-1P 141537-36-2P 141537-37-3P 141537-38-4P
141537-39-5P 141537-40-8P 141537-41-9P 141537-42-0P
141537-43-1P 141537-44-2P 141537-45-3P 141537-46-4P
141537-47-5P 141537-48-6P 141537-49-7P 141537-50-0P
141537-51-1P 141537-52-2P 141537-53-3P 141537-54-4P
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141537-59-9P 141537-60-2P 141537-61-3P 141537-62-4P
141537-63-5P 141537-64-6P 141537-65-7P 141537-66-8P
141537-67-9P 141537-68-0P 141537-69-1P 141537-70-4P
141537-71-5P 141537-72-6P 141537-73-7P 141537-74-8P
141537-75-9P 141537-76-0P 141537-77-1P 141537-78-2P
141537-79-3P 141537-80-6P 141537-81-7P
RL: SPN (Synthetic preparation); PREP (Preparation)
(preparation of, as intermediate for cyclic peptide antibiotic)

IT 75-36-5, Acetyl chloride 98-59-9, Tosyl chloride 98-88-4, Benzoyl chloride 99-96-7, reactions 104-15-4, reactions 106-21-8 111-83-1, 1-Bromooctane 355-80-6, 2,2,3,3,4,4,5,5-Octafluoropentanol 524-38-9, N-Hydroxyphthalimide 602-94-8, 2,3,4,5,6-Pentafluorobenzoic acid 626-64-2, 4-Hydroxypyridine 3417-91-2, Tyrosine methyl ester hydrochloride 16712-64-4, 6-Hydroxy-2-naphthoic acid 22118-09-8, 2-Bromoacetyl chloride 22818-40-2 24083-13-4, 4-Octyloxybenzaldehyde 34619-03-9, Di-tert-butylcarbonate 74124-79-1, N,N'-Disuccinimidyl carbonate 91868-79-0
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in preparation of cyclic peptide antibiotic)

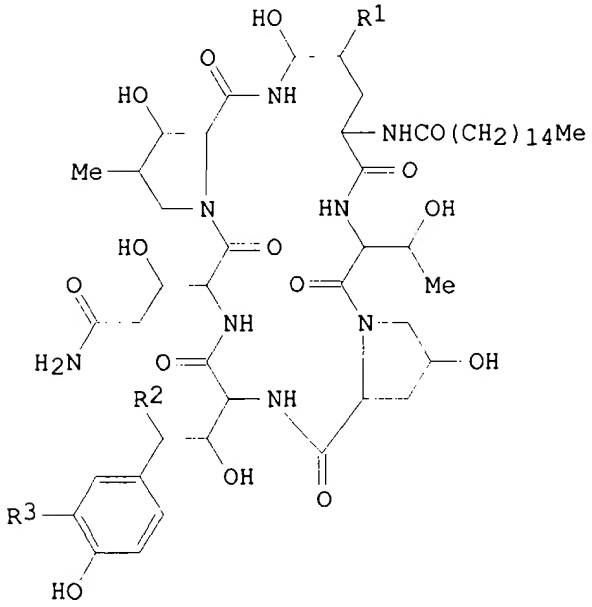
IT 2488-14-4
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, in preparation of cyclic polypeptide antibiotic)

L33 ANSWER 27 OF 27 MARPAT COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 116:57522 MARPAT
TITLE: Antifungal cyclic peptides from Coleophoma

INVENTOR(S): Iwamoto, Toshiro; Fujie, Akihiko; Nitta, Kumiko; Tsurumi, Yasuhisa; Shigematsu, Nobuharu; Kasahara, Chiyoshi; Hino, Motohiro; Okuhara, Masakuni
PATENT ASSIGNEE(S): Japan
SOURCE: Can. Pat. Appl., 35 pp.
CODEN: CPXXEB
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CA 2029766	AA	19910514	CA 1990-2029766	19901113
ZA 9008892	A	19910925	ZA 1990-8892	19901106
JP 03184921	A2	19910812	JP 1990-305797	19901108
JP 3111470	B2	20001120		
EP 431350	A1	19910612	EP 1990-121558	19901110
EP 431350	B1	19950726		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE				
ES 2075115	T3	19951001	ES 1990-121558	19901110
NO 9004904	A	19910514	NO 1990-4904	19901112
HU 58820	A2	19920330	HU 1990-7105	19901112
AU 9066557	A1	19910516	AU 1990-66557	19901113
CN 1051757	A	19910529	CN 1990-109271	19901113
US 5502033	A	19960326	US 1994-218883	19940328
PRIORITY APPLN. INFO.:			GB 1989-25593	19891113
			US 1990-610759	19901108

GI



I

AB Novel cyclic peptide antibiotics I (R1, R2 = H, OH, R3 = OH, hydroxysulfonyloxy; when R1 = H, R2 = H), active against fungi, are manufactured by fermentation of Coleophoma F-11899. Culture filtrates from Coleophoma F-11899 grown in a complex medium (dextran/glucose/wheat germ/cottonseed flour/salts) at 25° for 4 days were mixed with an equal volume of Me2CO and concentrated The concentrate was extd with two vols. EtOAc followed by BuOH and the BuOH extract fractionated chromatog. to yield a compound (containing a major and two minor components) active against Candida.

IC ICM C12P021-04
ICS C07K007-56; C12N001-20; A61K037-02

CC 16-2 (Fermentation and Bioindustrial Chemistry)
Section cross-reference(s): 1, 10

ST fungicide manuf Coleophoma; peptide cyclic fungicide Coleophoma

IT Coleophoma
(fungicidal compds. manufacture with)

IT Fermentation
(fungicidal compds., with Coleophoma)

IT Molecular structure, natural product
(of FR133302 (cyclic peptide))

IT Molecular structure, natural product
(of FR901379 (cyclic peptide))

IT Molecular structure, natural product
(of FR901381 (cyclic peptide))

IT Molecular structure, natural product
(of FR901382 (cyclic peptide))

IT Fungicides and Fungistats
(of Coleophoma)

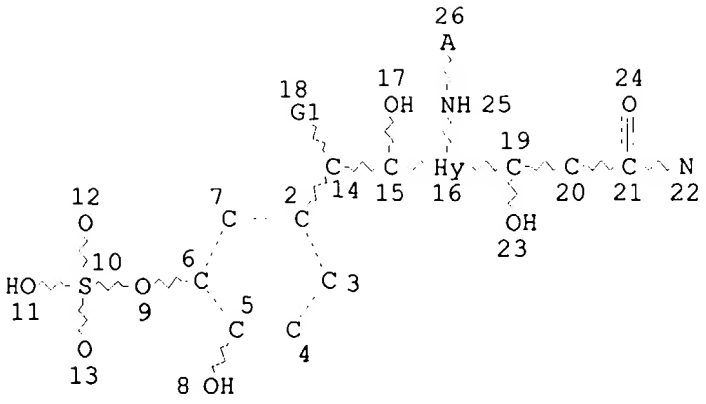
IT 9068-67-1, Sulfatase
RL: BIOL (Biological study)
(in FR133302 preparation from FR901379 of Coleophoma)

IT 138328-76-4P, FR 133302
RL: BMF (Bioindustrial manufacture); BIOL (Biological study); PREP (Preparation)
(manufacture of, from FR901379 of Coleophoma, with sulfatase)

IT 138328-74-2P, FR 901379 138328-75-3P, FR 901381 138626-86-5P, FR 901382
RL: BMF (Bioindustrial manufacture); BIOL (Biological study); PREP (Preparation)
(manufacture of, with Coleophoma)

FILE 'MARPATPREV' ENTERED AT 15:15:40 ON 22 OCT 2003

L31 STR



VAR G1=H/OH
NODE ATTRIBUTES:
NSPEC IS RC AT 26
CONNECT IS X2 RC AT 3
CONNECT IS X2 RC AT 4
CONNECT IS X2 RC AT 7
DEFAULT MLEVEL IS ATOM
MLEVEL IS CLASS AT 16
DEFAULT ECLEVEL IS LIMITED

GRAPH ATTRIBUTES:
RING(S) ARE ISOLATED OR EMBEDDED
NUMBER OF NODES IS 25

STEREO ATTRIBUTES: NONE

ATTRIBUTES SPECIFIED AT SEARCH-TIME:
ECLEVEL IS LIM ON ALL NODES
ALL RING(S) ARE ISOLATED

L34 0 SEA FILE=MARPATPREV SSS FUL L31 (MODIFIED ATTRIBUTES)

100.0% PROCESSED 4 ITERATIONS 0 ANSWERS
SEARCH TIME: 00.00.01

FILE 'HOME' ENTERED AT 15:15:58 ON 22 OCT 2003

(FILE 'HCAPLUS' ENTERED AT 15:03:01 ON 22 OCT 2003)

L6	7	SEA FILE=REGISTRY ABB=ON PLU=ON (FLUCONAZOLE OR VORICONAZOLE OR ITRACONAZOLE OR KETOCONAZOLE OR MICONAZOLE OR AMPHOTERICIN B)/CN
L7	1	SEA FILE=REGISTRY ABB=ON PLU=ON "ER 30346"/CN
L8	1	SEA FILE=REGISTRY ABB=ON PLU=ON "SCH 56592"/CN
L9	4	SEA FILE=REGISTRY ABB=ON PLU=ON (NYSTATIN OR FLUCYTOSINE OR NIKKOMYCIN X OR PREDAMYCIN)/CN
L10	1	SEA FILE=REGISTRY ABB=ON PLU=ON SORDARIN/CN
L11	14	SEA FILE=REGISTRY ABB=ON PLU=ON L6 OR L7 OR L8 OR L9 OR L10
L20	1704	SEA FILE=HCAPLUS ABB=ON PLU=ON LIPOPEPTIDE OR LIPO PEPTIDE
L21	9	SEA FILE=HCAPLUS ABB=ON PLU=ON L20 AND (AMPHB OR AMPH B OR FLCZ OR VRC OR AMB OR LAMB OR ITCZ OR KCZ)
L22	517	SEA FILE=HCAPLUS ABB=ON PLU=ON L20 AND (L11 OR FLUCONAZOLE OR VORICONAZOLE OR ITRACONAZOLE OR KETOCONAZOLE OR MICONAZOLE OR ER30346 OR ER 30346 OR SCH56592 OR SCH 56592 OR AMPHOTERICIN B OR NYSTATIN OR FLUCYTOSINE OR NIKKOMYCIN X OR PREDAMYCIN OR SORDARIN OR LIPOSOM## OR LIPID)
L23	126	SEA FILE=HCAPLUS ABB=ON PLU=ON (L21 OR L22) AND (THERAP? OR TREAT? OR PROPHYLACT? OR PROPHYLAX? OR PREVENT?)
L24	23	SEA FILE=HCAPLUS ABB=ON PLU=ON L23 AND (CRYPTOCOCC? OR CANDIDA OR ASPERGILLUS OR HISTOPLASMA OR COCCIDIOIDES OR PARACOCCIDIOIDES OR BLASTOMYCES OR FUSARIUM OR SPOROTHRIX OR TRICHOSPORON OR RHIZOPUS OR PSEUDALLESCHER? OR DERMATOPHYT? OR PAECILIOMYES OR ALTERNARIA)

-key terms

(FILE 'HCAPLUS' ENTERED AT 15:03:01 ON 22 OCT 2003)

L6 7 SEA FILE=REGISTRY ABB=ON PLU=ON (FLUCONAZOLE OR VORICONAZOLE OR ITRACONAZOLE OR KETOCONAZOLE OR MICONAZOLE OR AMPHOTERICIN B)/CN

L7 1 SEA FILE=REGISTRY ABB=ON PLU=ON "ER 30346"/CN

L8 1 SEA FILE=REGISTRY ABB=ON PLU=ON "SCH 56592"/CN

L9 4 SEA FILE=REGISTRY ABB=ON PLU=ON (NYSTATIN OR FLUCYTOSINE OR NIKKOMYCIN X OR PREDAMYCIN)/CN

L10 1 SEA FILE=REGISTRY ABB=ON PLU=ON SORDARIN/CN

L11 14 SEA FILE=REGISTRY ABB=ON PLU=ON L6 OR L7 OR L8 OR L9 OR L10

L20 1704 SEA FILE=HCAPLUS ABB=ON PLU=ON LIPOPEPTIDE OR LIPO PEPTIDE

L21 9 SEA FILE=HCAPLUS ABB=ON PLU=ON L20 AND (AMPHB OR AMPH B OR FLCZ OR VRC OR AMB OR LAMB OR ITCZ OR KCZ)

L22 517 SEA FILE=HCAPLUS ABB=ON PLU=ON L20 AND (L11 OR FLUCONAZOLE OR VORICONAZOLE OR ITRACONAZOLE OR KETOCONAZOLE OR MICONAZOLE OR ER30346 OR ER 30346 OR SCH56592 OR SCH 56592 OR AMPHOTERICIN B OR NYSTATIN OR FLUCYTOSINE OR NIKKOMYCIN X OR PREDAMYCIN OR SORDARIN OR LIPOSOM## OR LIPID)

L23 126 SEA FILE=HCAPLUS ABB=ON PLU=ON (L21 OR L22) AND (THERAP? OR TREAT? OR PROPHYLACT? OR PROPHYLAX? OR PREVENT?)

L25 16 SEA FILE=HCAPLUS ABB=ON PLU=ON L23 AND (CURVULARIA OR EXOPHIALA OR WANGIELLA OR PENICILLIUM OR SACCHAROMYCES OR DEMATIAC? OR CARINII OR ASPERGILLUS)

L26 17 (L24 OR L25) NOT L13

L26 ANSWER 1 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 2003:786874 HCAPLUS

TITLE: Echinocandin antifungal drugs

AUTHOR(S): Denning, David W.

CORPORATE SOURCE: Education and Research Centre, Wythenshawe Hospital, Southmoor Road, Manchester, M23 9LT

SOURCE: Lancet (2003), 362(9390), 1142-1151
CODEN: LANCAO; ISSN: 0140-6736

PUBLISHER: Elsevier Science Ltd.

DOCUMENT TYPE: Journal

LANGUAGE: English

AB The echinocandins are large **lipopeptide** mols. that are inhibitors of β-(1,3)-glucan synthesis, an action that damages fungal cell walls. In vitro and in vivo, the echinocandins are rapidly fungicidal against most **Candida** spp and fungistatic against **Aspergillus** spp. They are not active at clin. relevant concns. against Zygomycetes, **Cryptococcus** neoformans, or Fusarium spp. No drug target is present in mammalian cells. The first of the class to be licensed was caspofungin, for refractory invasive aspergillosis (about 40% response rate) and the second was micafungin. Adverse events are generally mild, including (for caspofungin) local phlebitis, fever, abnormal liver function tests, and mild haemolysis. Poor absorption after oral administration limits use to the i.v. route. Dosing is once daily and drug interactions are few. The echinocandins are widely distributed in the body, and are metabolised by the liver. Results of studies of caspofungin in candidemia and invasive candidiasis suggest equivalent efficacy to **amphotericin B**, with

substantially fewer toxic effects. Absence of antagonism in combination with other antifungal drugs suggests that combination antifungal **therapy** could become a general feature of the echinocandins, particularly for invasive aspergillosis.

L26 ANSWER 2 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:704649 HCAPLUS
TITLE: Antifungal **lipopeptides**: a tale of *pseudomycin prodrugs and analogues*
AUTHOR(S): Chen, Shu-Hui; Rodriguez, Michael
CORPORATE SOURCE: Lilly Research Laboratories, Lilly Corporate Center, Eli Lilly and Company, Indianapolis, IN, 46285, USA
SOURCE: Drugs of the Future (2003), 28(5), 441-463
CODEN: DRFUD4; ISSN: 0377-8282
PUBLISHER: Prous Science
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Systemic fungal infections (SFI) can cause serious life-threatening diseases in normal healthy humans. **Candida** albicans, **Cryptococcus** neoformans and **Aspergillus** fumigatus are the major opportunistic pathogens responsible for SFI. The rising incidence of SFI, especially in immunocompromised patients, attests to the need for more effective **therapies**. Present **treatment** options are limited to three classes of compds., the polyenes, the azoles and the recently approved **lipopeptide** caspofungin acetate. **Amphotericin B** and azole-based antifungal agents have an inadequate spectrum of activity and rapid emergence of fungal resistance, limited dosage forms and a narrow **therapeutic** window. Several approaches have been taken to address these deficiencies, such as improving the biol. and/or toxicol. profiles of existing drugs or the search for novel antifungal **lipopeptides**. As a result of this search, several cyclic peptides endowed with promising antifungal activities have been identified, including aureobasidins, echinocandins, papulacandin B and the recently disclosed pseudomycins. The most significant progress on this front was the 2001 launch of caspofungin acetate in the U.S. for the parenteral **treatment** of invasive aspergillosis in patients refractory to or intolerant of other antifungal **therapies**. This review provides a brief update on a number of recently discovered antifungal **lipopeptides**, as well as structural modifications and evaluation of pseudomycin analogs and prodrugs.
REFERENCE COUNT: 98 THERE ARE 98 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 3 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:536586 HCAPLUS
DOCUMENT NUMBER: 139:206927
TITLE: Anidulafungin: ECB, LY 303366, V-echinocandin, VEC, VER 002, VER-02
AUTHOR(S): Anon.
CORPORATE SOURCE: N. Z.
SOURCE: Drugs in R&D (2003), 4(3), 167-173
CODEN: DRDDFD; ISSN: 1174-5886
PUBLISHER: Adis International Ltd.
DOCUMENT TYPE: Journal; General Review

LANGUAGE: English

AB A review. Vicuron Pharmaceuticals (formerly Versicor Inc.) is developing anidulafungin [LY 303366, ECB, V-echinocandin, VEC, VER-02, VER 002], a **lipopeptide** echinocandin B derivative, for i.v. **treatment** of mycoses. Anidulafungin acts against fungal infection by inhibiting β-1,3-glucan synthase, an enzyme essential for cell wall formation. Anidulafungin was originally developed for oral use by Eli Lilly and was undergoing phase II clin. trials in the UK and the US for the **treatment** of **Candida**, **Aspergillus** and *Pneumocystis* **carinii** infections. However, Eli Lilly discontinued development of the oral formulation due to poor oral bioavailability. In May 1999, Versicor obtained exclusive worldwide commercialization rights to anidulafungin with responsibility for its development and clin. registration. Under the terms of the agreement, Eli Lilly received a signing fee, and will receive milestone payments upon future development of anidulafungin and royalties on future sales. Eli Lilly also retains an option for the development of an oral formulation of the compound On 3 Mar. 2003, Versicor Inc. of Fremont, California, USA, and Biosearch Italia SpA of Milan, Italy, announced the completion of a merger agreement, whereby Biosearch was merged with and into Versicor in a stock-for-stock exchange valued at $US260.7 million. The combined company temporarily kept the name Versicor until the new name, Vicuron Pharmaceuticals, was announced on 26 Mar. 2003. In Jan. 2003, Versicor announced that pos. results from a phase II trial for anidulafungin i.v. **treatment** involving 120 patients in the US with invasive candidiasis/candidemia, have led to another double-blind, randomized phase III trial being conducted in the US, Canada and Europe for this indication. This addnl. phase III trial will enroll approx. 300 patients to investigate the efficacy of i.v. anidulafungin (200 mg loading dose followed by 100 mg maintenance dose) vs. i.v. **fluconazole** for 10-42 days. Vicuron Pharmaceuticals also plans to seek approval for **treatment** of invasive candidiasis/candidemia in Europe and Canada in the 2nd half of 2003.

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 4 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2003:77719 HCAPLUS
DOCUMENT NUMBER: 138:135825
TITLE: **Therapeutic** application of HIV-1 Tat protein
INVENTOR(S): Ensoli, Barbara
PATENT ASSIGNEE(S): Istituto Superiore di Sanita, Italy
SOURCE: Eur. Pat. Appl., 98 pp.
CODEN: EPXXDW
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
EP 1279404	A1	20030129	EP 2001-118114	20010726
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC,				

PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
WO 2003009867 A1 20030206 WO 2002-EP8377 20020726
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG
PRIORITY APPLN. INFO.: EP 2001-118114 A 20010726

AB The author discloses vaccination, **treatment**, and diagnosis of HIV/AIDS and other infectious diseases, inflammatory and angiogenic diseases and tumors utilizing a biol. active HIV-1 Tat protein or fragments or derivs. thereof. The author discloses that Tat and Tat fragments can be characterized with one or more of the following features: as antigen, as adjuvant and targeting-delivery system to specific antigen-presenting cells including dendritic cells, endothelial cells and macrophages.

REFERENCE COUNT: 6 THERE ARE 6 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 5 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2002:964121 HCAPLUS
DOCUMENT NUMBER: 138:44697
TITLE: Polyvalent nanoparticles for diagnosis and **therapy**
INVENTOR(S): Nagy, Jon O.; Bargatze, Robert F.; Jutila, John W.; Cutler, Jim E.; Han, Yongmoon; Glee, Pati M.; Pascual, David
PATENT ASSIGNEE(S): Ligocyte Pharmaceuticals, Inc., USA; Montana State University-Bozeman
SOURCE: PCT Int. Appl., 56 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002100325	A2	20021219	WO 2001-US42712	20011015
WO 2002100325	A3	20030724		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-239874P P 20001013

AB The authors disclose nanoparticles comprised of a carrier, particularly polymerized **lipids**, and ligands displayed on the carrier, wherein the ligands form a polyvalent binding unit that is effective to produce a specific interaction between the nanoparticle and receptors on a target, particularly under physiol. relevant shear conditions. In one example, a first ligand is sialyl Lewis x oligosaccharide and a second ligand is an organic acid-based charged head group. The polyvalent nanoparticles inhibit selectin-dependent adherence of leukocytes.

L26 ANSWER 6 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:671259 HCAPLUS
DOCUMENT NUMBER: 135:352261
TITLE: Caspofungin: pharmacology, safety and **therapeutic** potential in superficial and invasive fungal infections
AUTHOR(S): Groll, Andreas H.; Walsh, Thomas J.
CORPORATE SOURCE: Immunocompromised Host Section, Pediatric Oncology Branch, National Cancer Institute, Bethesda, MD, USA
SOURCE: Expert Opinion on Investigational Drugs (2001), 10(8), 1545-1558
CODEN: EOIDER; ISSN: 1354-3784
PUBLISHER: Ashley Publications Ltd.
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English

AB A review with refs. Invasive fungal infections are important causes of morbidity and mortality in hospitalized patients. Current **therapy** with **amphotericin B** and antifungal triazoles has overlapping targets and is limited by toxicity and resistance. The echinocandin **lipopeptide** caspofungin is the first of a new class of antifungal compds. that inhibit the synthesis of 1,3-β-D-glucan. This homopolysaccharide is a major component of the cell wall of many pathogenic fungi and yet is absent in mammalian cells. It provides osmotic stability and is important for cell growth and cell division. In vitro, caspofungin has broad-spectrum antifungal activity against **Candida** and **Aspergillus** spp. without cross-resistance to existing agents. The compound exerts prolonged post-antifungal effects and fungicidal activity against **Candida** species and causes severe damage of **Aspergillus** fumigatus at the sites of hyphal growth. Animal models have demonstrated efficacy against disseminated candidiasis and disseminated and pulmonary aspergillosis, both in normal and in immunocompromised animals. Caspofungin possesses favorable pharmacokinetic properties and is not metabolized through the CYP450 enzyme system. It showed highly promising antifungal efficacy in Phase II and III clin. trials in immunocompromised patients with oesophageal candidiasis. Caspofungin was effective in patients with invasive aspergillosis intolerant or refractory to standard **therapies**. Based on its documented antifungal efficacy and an excellent safety profile, caspofungin has been approved recently by the US Food and Drug Administration for the **treatment** of invasive aspergillosis in patients who are refractory to or intolerant of other **therapies** (i.e., **amphotericin B**, **lipid** formulations of **amphotericin B**, and/or **itraconazole**). Phase III clin. trials

in patients with candidemia and in persistently febrile neutropenic patients requiring empirical antifungal **therapy** are ongoing. This paper reviews the preclin. and clin. pharmacol. of caspofungin and its potential role for **treatment** of invasive and superficial fungal infections in patients.
REFERENCE COUNT: 66 THERE ARE 66 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 7 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2001:42558 HCAPLUS
DOCUMENT NUMBER: 135:86351
TITLE: New developments in **therapy** of deep mycoses
AUTHOR(S): Yamaguchi, Hideyo
CORPORATE SOURCE: Teikyo University Institute of Medical Mycology, Hachioji, 192-0395, Japan
SOURCE: Nippon Ishinkin Gakkai Zasshi (2000), 41(4), 221-228
CODEN: NIGZE4; ISSN: 0916-4804
PUBLISHER: Nippon Ishinkin Gakkai
DOCUMENT TYPE: Journal; General Review
LANGUAGE: Japanese
AB A review with 59 refs. Over the past two decades the incidence of deep mycoses caused by several major groups of fungal pathogens such as **Candida** spp., **aspergilli**, **Cryptococcus** neoformans and zygomycetes has risen steadily. Moreover, opportunistic fungal infections due to Fusarium spp., **Trichosporon** spp., **Pseudallescheria** boydii and other emerging pathogens, as well as **fluconazole**-resistant **Candida** albicans, all of which are often resistant to existing antifungal drugs, are also encountered more and more frequently. This makes it more difficult for the clinician to achieve successful **treatment**. Thus there is an urgent need to develop new antifungal agents or formulations with advantages over and/or complimentary to existing drugs. This review focuses on current approaches to antifungal chemotherapy with special reference to the clin. development of new drugs, including (ii) **lipid** formulations of **amphotericin B**, (i) second-generation azoles and (iii) antifungal **lipopeptides**.

L26 ANSWER 8 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 2000:276136 HCAPLUS
DOCUMENT NUMBER: 133:55907
TITLE: In vitro activity of A-192411.29, a novel antifungal **lipopeptide**
AUTHOR(S): Nilius, Angela M.; Raney, Patti M.; Hensey-Rudloff, Dena M.; Wang, Weibo; Li, Qun; Flamm, Robert K.
CORPORATE SOURCE: Infectious Diseases Research, Abbott Laboratories, Abbott Park, IL, 60064-3537, USA
SOURCE: Antimicrobial Agents and Chemotherapy (2000), 44(5), 1242-1246
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A-192411.29 is a novel antifungal agent derived from the structural template of the natural product echinocandin. The in vitro activity of A-192411.29 against common pathogenic yeasts was assessed by National Committee for Clin. Laboratory Stds. method M27-A. It demonstrated broad-spectrum, fungicidal activity and was active against the most clin. relevant yeasts, such as **Candida** albicans, **Candida** tropicalis, and **Candida** glabrata, as well as less commonly encountered **Candida** species; in general, its potency on a weight basis was comparable to that of **amphotericin B**. It maintained potent in vitro activity against **Candida** strains with reduced susceptibilities to **fluconazole** and **amphotericin B**. The in vitro activity of A-192411.29 against **Cryptococcus** neoformans was comparable to its activity against **Candida** spp. However, A-192411.29 did not demonstrate complete growth inhibition of **Aspergillus** fumigatus by the broth microdilution method used. A-192411.29 possesses an antifungal profile comparable to or better than those of **fluconazole** and **amphotericin B** against pathogenic yeast, including strains resistant to **fluconazole** or **amphotericin B**, suggesting that it may be a **therapeutically** useful new antifungal drug.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 9 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1999:240392 HCAPLUS
DOCUMENT NUMBER: 131:29717
TITLE: LY303366 exhibits rapid and potent fungicidal activity in flow cytometric assays of yeast viability
AUTHOR(S): Green, Lisa J.; Marder, Philip; Mann, Larry L.; Chio, Li-Chun; Current, William L.
CORPORATE SOURCE: Lilly Corporate Center, Lilly Research Laboratories, Indianapolis, IN, 46285, USA
SOURCE: Antimicrobial Agents and Chemotherapy (1999), 43(4), 830-835
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB LY303366 is a semisynthetic analog of the antifungal **lipopeptide** echinocandin B that inhibits (1,3)-β-D-glucan synthase and exhibits efficacy in animal models of human fungal infections. In this study, the authors utilized flow cytometric anal. of propidium iodide uptake, single-cell sorting, and standard microbiol. plating methods to study the antifungal effect of LY303366 on **Saccharomyces** cerevisiae and **Candida** albicans. The data indicate that an initial 5-min pulse **treatment** with LY303366 caused yeasts to take up propidium iodide and lose their ability to grow. **Amphotericin B** and cilofungin required longer exposure periods (30 and 180 min, resp.) and higher concns. to elicit these fungicidal effects. These two measurements of fungicidal activity by LY303366 were highly correlated ($r > 0.99$) in concentration response and time course expts. As further validation,

LY303366-**treated** yeasts that stained with propidium iodide were unable to grow in single-cell-sorted cultures. The data indicate that LY303366 is potent and rapidly fungicidal for actively growing yeasts. The potency and rapid action of this new fungicidal compound suggest that LY303366 may be useful for antifungal **therapy**.

REFERENCE COUNT: 32 THERE ARE 32 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 10 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:402716 HCAPLUS
DOCUMENT NUMBER: 125:104145
TITLE: New model of oropharyngeal and gastrointestinal colonization by **Candida** albicans in CD4+ T-cell-deficient mice for evaluation of antifungal agents
AUTHOR(S): Flattery, Amy M.; Abruzzo, George K.; Gill, Charles J.; Smith, Jeffrey G.; Bartizal, Ken
CORPORATE SOURCE: Antibiotic Discovery and Development, Merck Research laboratories, Rahway, NJ, 07065-0900, USA
SOURCE: Antimicrobial Agents and Chemotherapy (1996), 40(7), 1604-1609
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English

AB A new model for the evaluation of antifungal compds. against oropharyngeal and gastrointestinal mucosal colonization by **Candida** albicans was developed. To simulate the immune deficiency observed in AIDS patients, mice were depleted of CD4+ T lymphocytes by the injection of either GK1.5 hybridoma cells or purified anti-CD4+ monoclonal antibody derived from GK1.5 hybridoma cells in tissue culture. Fluorescence-activated cell sorter anal. of splenic lymphocytes confirmed the elimination of the CD4+ T-cell population. Gentamicin, a broad-spectrum, non-absorbable aminoglycoside antibiotic, was given via the drinking water to reduce the normal gastrointestinal microflora, allowing less competition for colonization of the gastrointestinal tract by the C. albicans isolates. Mice were challenged by gavage and swabbing their oral mucosa with a pure culture of C. albicans. Gentamicin was withdrawn 3 days post-challenge, and antifungal compds. were administered via the drinking water ad libitum at concns. ranging from 25-400 μg/mL. L-693989, a water-soluble phosphorylated cyclic **lipopeptide** prodrug of pneumocandin Bo, and L-733560, a semisynthetic derivative of pneumocandin Bo, are inhibitors of 1,3-β-D-glucan synthesis that exhibit potent in vivo anti-**Candida** spp. and anti-Pneumocystis **carinii** activities. The efficacies of L-693989, L-733560, **fluconazole**, **ketoconazole**, and **nystatin** were evaluated in this new oropharyngeal and gastrointestinal model of mucosal colonization. L-693989, L-733560, **fluconazole**, and **ketoconazole** showed superior efficacies in reducing the nos. of C. albicans CFU per g of feces and the nos. of oral CFU relative to those in sham-**treated** controls in this model, while **nystatin** was moderately effective in reducing oral and fecal colonization by C. albicans in this model.

IT **1400-61-9, Nystatin 65277-42-1,**
Ketoconazole 86386-73-4, Fluconazole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(new model of oropharyngeal and gastrointestinal colonization by **Candida** albicans in CD4+ T-cell-deficient mice for evaluation of antifungal agents)

L26 ANSWER 11 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1996:375891 HCAPLUS
DOCUMENT NUMBER: 125:48125
TITLE: Recent advances in the medicinal chemistry of antifungal agents
AUTHOR(S): Turner, W. W.; Rodriguez, M. J.
CORPORATE SOURCE: Lilly Research Labs., Division Eli Lilly and Company, Indianapolis, IN, 46285, USA
SOURCE: Current Pharmaceutical Design (1996), 2(2), 209-224
CODEN: CPDEFP; ISSN: 1381-6128
PUBLISHER: Bentham Science Publishers
DOCUMENT TYPE: Journal; General Review
LANGUAGE: English
AB A review, with 79 refs., on the search for effective antifungal agents to combat serious systemic infections. Present **therapeutic** options for the **treatment** of these infections are limited to compds. in two classes, the polyenes and the azoles. Some polyene research still continues with analogs of **amphotericin B** in the hopes of decreasing toxicity. Much work continues in the azole area with follow-up compds. to **fluconazole** and **itraconazole** in order to expand the spectrum and provide oral and i.v. formulation potential. A newer class of cell wall active agents that has been developed to the point of seeing clin. candidates is the cyclic **lipopeptide** echinocandin family. This group has the potential of providing broad spectrum fungicidal activity with a much lower toxicity level than the current agents. Another newer class of natural products known as the aureobasidins has potent, oral fungicidal activity against **Candida** spp. Research has continued with the pradimicins to produce several new semisynthetic derivs. with comparable activity and spectrum to the parent compound but with improved water-solubility Work with the nikkomycin class had delineated points of the SAR but has not produced compds. of sufficient potency for clin. use. The allylamines have been examined further to provide analogs of terbinafine with increased **Candida** activity but are still most highly potent vs. **dermatophytes**. Several other newer classes with unique mechanisms of action have also been identified.

L26 ANSWER 12 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1995:540612 HCAPLUS
DOCUMENT NUMBER: 123:25238
TITLE: Evaluation of water-soluble pneumocandin analogs L-733560, L-705589, and L-731373 with mouse models of disseminated aspergillosis, candidiasis, and **cryptococcosis**
AUTHOR(S): Abruzzo, George K.; Flattery, Amy M.; Gill, Charles J.; Kong, Li; Smith, Jeffrey G.; Krupa,

David; Pikounis, V. Bill; Kropp, Helmut; Bartizal, Kenneth
CORPORATE SOURCE: Antibiotic Discovery Dev., Merck Res. Labs., Rahway, NJ, 07065-0900, USA
SOURCE: Antimicrobial Agents and Chemotherapy (1995), 39(5), 1077-81
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The activities of the water-soluble pneumocandin derivs. L-733560, L-705589, and L-731373 were evaluated in mouse models of disseminated aspergillosis, candidiasis, and **cryptococcosis** and were compared with those of com. available antifungal agents. Pneumocandins are inhibitors of 1,3-β-D-glucan synthesis. In the aspergillosis model, L-733560 and L-705589 significantly prolonged the survival of DBA/2N mice challenged i.v. with **Aspergillus** fumigatus conidia. L-733560 and L-705589 exhibited efficacies comparable to that of **amphotericin B** (**AMB**) with 90% EDs of 0.48, 0.12, and 0.36 mg/kg of body weight, resp. Two mouse models of disseminated candidiasis were used to evaluate these compds. In both models, mice were challenged i.v. with **Candida** albicans. In a C. albicans survival model with DBA/2N and CD-1 mice, the efficacy of L-733560 was comparable to that of **AMB**, while L-731373 and L-705589 were somewhat less active. In a previously described C. albicans target organ kidney assay, the pneumocandin analogs and **AMB** at doses of ≥0.09 mg/kg were effective in sterilizing kidneys, while **fluconazole** and **ketoconazole** were considerably less active and did not sterilize kidneys when they used at concns. of ≤100 mg/kg. Although orally administered L-733560 showed activity in both candidiasis models, its efficacy was reduced compared with that of parenterally administered drug. In a disseminated **cryptococcosis** mouse model that measures the number of CFU of **Cryptococcus** *neoformans per g of brain* and spleen, L-733560 at 10 mg/kg was ineffective in reducing the counts in organs, while **AMB** at 0.31 mg/kg, sterilized the organs. These results indicate that the pneumocandins may be beneficial as potent parenterally administered **therapeutic** agents for disseminated aspergillosis and candidiasis.

L26 ANSWER 13 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1995:244826 HCAPLUS
DOCUMENT NUMBER: 122:95906
TITLE: Increased antifungal activity of L-733,560, a water-soluble, semisynthetic pneumocandin, is due to enhanced inhibition of cell wall *synthesis*
AUTHOR(S): Kurtz, M. B.; Douglas, C.; Marrinan, J.; Nollstadt, K.; Onishi, J.; Dreikorn, S.; Milligan, J.; Mandala, S.; Thompson, J.; et al.
CORPORATE SOURCE: Infectious Disease Res., Antibiotic Evaluation, Rahway, NJ, 07065, USA
SOURCE: Antimicrobial Agents and Chemotherapy (1994), 38(12), 2750-7
CODEN: AMACCQ; ISSN: 0066-4804
PUBLISHER: American Society for Microbiology
DOCUMENT TYPE: Journal

LANGUAGE: English

AB The pneumocandins are natural **lipopeptide** products of the echinocandin class which inhibit the synthesis of 1,3-β-D-glucan in susceptible fungi. The lack of a corresponding pathway in mammalian hosts makes this mode of action an attractive one for **treating** systemic infections. Substitution by an aminoethyl ether at the hemiaminal and dehydration and reduction of the glutamine of pneumocandin Bo produced a semisynthetic compound (L-733,560) with intrinsic water solubility, significantly increased potency, and a broader antifungal spectrum. To evaluate the mechanism for the improved antifungal efficacy, we determined that L-733,560 was a more potent inhibitor of glucan synthase activity in vitro, did not affect the other membrane-bound enzymes tested, conferred susceptibility to lysis in the absence of osmotic support, and did not disrupt currents in **liposomal** bilayers or 86Rb+ fluxes from **liposomes**. In **Aspergillus** species L-733,560 also produced the same morphol. alterations as pneumocandin Bo. A stereoisomer of L-733,560 with poor antifungal activity was a weak inhibitor of glucan synthase. All of these results support the notion that the enhanced antifungal activity of L-733,560 is achieved by superior inhibition of glucan synthesis and not by nonspecific membrane effects or a second mode of action.

L26 ANSWER 14 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1993:225034 HCAPLUS
DOCUMENT NUMBER: 118:225034
TITLE: Comparative efficacies of cilofungin (Ly121019) and **amphotericin B** against disseminated **Candida** albicans infection in normal and granulocytopenic mice
AUTHOR(S): Khardori, Nancy; Hieu, Nguyen; Stephens, L. Clifton; Kalvakuntla, Laxman; Rosenbaum, Beverly; Bodey, G. P.
CORPORATE SOURCE: M.D. Anderson Cancer Cent., Univ. Texas, Houston, TX, 77030, USA
SOURCE: Antimicrobial Agents and Chemotherapy (1993), 37(4), 729-36
CODEN: AMACCQ; ISSN: 0066-4804
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The efficacies of cilofungin (Ly121019), a semisynthetic **lipopeptide** antifungal agent, and **amphotericin B** in the **treatment** of disseminated candidiasis in normal and neutropenic mice were compared. In mice infected with 2 + 106 CFU of C. albicans, **treatment** with cilofungin in twice-daily doses of 25 or 35 mg/kg of body weight by i.p. injection for 10 days gave survival rates of 83 and 90%. In contrast, there was 97% mortality in infected controls receiving 2 + 106 CFU i.v. and 93% survival in mice **treated** with 1 mg of **amphotericin B** per kg once a day. Mice rendered granulocytopenic by the administration of cyclophosphamide showed survival rates of 83 and 80% when **treated** with 25 or 35 mg of cilofungin per kg for 10 days compared with 43% survival rate in mice **treated** with 1 mg of **amphotericin B** per kg. Similar results were obtained when the two antifungal agents were administered for a period of 30 days. Administration of 25 or 35 mg of cilofungin per kg twice a day to granulocytopenic

mice receiving 106 CFU of C. albicans gave survival rates of 93% and 93% compared with 53% survival with **amphotericin B**. With 15 mg of cilofungin per kg twice a day for 10 days, a survival rate of 43 to 50% was observed in both normal and granulocytopenic mice compared with 56 and 60%, resp., when this dosage was continued for 30 days. Cilofungin eradicated C. albicans from the kidneys, spleens, and livers of surviving animals. No toxic effects were observed with any of the dosage regimens used. The clearance of C. albicans from the kidneys, spleens, livers and brains in normal mice was studied following injected with infection with 5 + 105 and 1 + 105 i.v. The mice in the **treatment** groups received 25 mg of cilofungin per kg twice a day for 10 days. In 8 to 12 days, this **treatment** was able to clear the organisms from the kidneys, spleens, and livers of mice infected with 5 + 105 C. albicans. Mice infected with 105 C. albicans and **treated** with cilofungin (25 mg/kg) twice a day for 10 days has no organisms in the kidney, spleen, and liver at days 8, 2, and 8, resp. There was 1-log-unit reduction in C. albicans counts in brain tissue from mice of one of the **treated** groups between 2 h and 2 days postinfection, after which the nos. of organisms remained the same until day 12. These data demonstrate the efficacy of cilofungin in the **treatment** of disseminated C. albicans infections in normal and granulocytopenic mice. The **treatment** regimen used in this study was able to clear C. albicans from the kidney, spleen, and liver but not from brain tissue.

IT **1397-89-3, Amphotericin B**
RL: BIOL (Biological study)
(disseminated **Candida** albicans infection **therapy** with cilofungin vs., in neutropenia)

L26 ANSWER 15 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1990:400205 HCAPLUS
DOCUMENT NUMBER: 113:205
TITLE: *Comparative effects of cilofungin and* **amphotericin B** on experimental murine candidiasis
AUTHOR(S): Morrison, Christine J.; Stevens, David A.
CORPORATE SOURCE: Santa Clara Valley Med. Cent., California Inst. Med. Res., San Jose, CA, 95128, USA
SOURCE: Antimicrobial Agents and Chemotherapy (1990), 34(5), 746-50
CODEN: AMACCQ; ISSN: 0066-4804
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effectiveness of cilofungin (LY121019, referred to hereafter as LY), a **lipopeptide**, was studied in a murine candidiasis *model. CD-1 mice were injected i.v. with* 3 + 105 **Candida** albicans yeast cells. I.p. LY or **amphotericin B** (**AmB**) **therapy** was begun 4 days after infection and was continued daily for 2 wk. LY and **AmB** were compared at 62.5, 6.25, and 0.625 mg/kg/day, with the LY dose split into 2 **treatments** per day. Mice were observed for 30 days postinfection, and survivors were necropsied. **AmB** at 62.5 mg/kg/day was lethal in the absence of infection. Cumulative mortality for infected controls was 94%. Survival of mice **treated** with the control diluent for LY was the same as survival with no **treatment**.

Survival after 0.625 mg of LY/kg/day was the same as that of the controls, and 6.25 or 62.5 mg of LY/kg/day was superior. **AmB treatment** at 0.625 or 6.25 mg/kg/day was protective and superior to the same LY doses. Atrophied kidneys were common in **AmB-treated** mice, and mice **treated** with 6.25 mg of **AmB**/kg/day appeared ill during **therapy**. The number of CFU recovered from kidneys and spleens of surviving mice reflected the same relationships between drugs and doses as those described for mortality. C. albicans was not cleared from the kidneys of mice in any group, and only in the 6.25-mg/kg/day **AmB treatment** group was no detectable C. albicans found in the spleens. These data indicate that LY and **AmB** suppress candidal infection but neither is curative in this model.

IT **1397-89-3, Amphotericin B**
RL: BIOL (Biological study)
(candidiasis **treatment** with cilofungin vs., kidney toxicity in)

L26 ANSWER 16 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN
ACCESSION NUMBER: 1989:420771 HCAPLUS
DOCUMENT NUMBER: 111:20771
TITLE: Comparative activity in vitro of cilofungin (LY 121019) with other agents used for **treatment** of deep-seated **Candida** infections
AUTHOR(S): Rennie, R. P.; Hellman, L.
CORPORATE SOURCE: Dep. Clin. Microbiol., Univ. Hosp., Saskatoon, SK, S7N OXO, Can.
SOURCE: Mycoses (1989), 32(3), 145-50
CODEN: MYCSEU; ISSN: 0933-7407
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cilofungin (LY 121019) is a semisynthetic **lipopeptide** antifungal agent that inhibits β-1,3-D-glucan synthase activity in the cell wall of yeasts. Clin. strains of **Candida** were tested for susceptibility to cilofungin and 7 other antifungal agents. C. albicans and C. tropicalis were susceptible to cilofungin with mean MICs of 0.3 and 0.08 μg/mL, resp. For most other species the mean MICs were >1-2 μg/mL of cilofungin. Studies on the paradoxical growth effect observed with cilofungin in Sabouraud broth showed that, at high concns. of cilofungin, sufficient damage occurred to make damaged cells highly susceptible to killing by fresh cilofungin. The damaged cells also had increased susceptibility to other antifungal agents to which they were normally resistant. These observations indicate that cilofungin may be a useful agent for the **treatment** of many invasive **Candida** infections, either alone or in combination with certain other antifungal agents.

IT **1397-89-3, Amphotericin B**
1400-61-9, Nystatin 2022-85-7,
5-Fluorocytosine **22916-47-8, Miconazole**
65277-42-1, Ketoconazole
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); BIOL (Biological study)
(**Candida** sensitivity to, cilofungin in relation to)

L26 ANSWER 17 OF 17 HCAPLUS COPYRIGHT 2003 ACS on STN

ACCESSION NUMBER: 1988:420176 HCAPLUS
DOCUMENT NUMBER: 109:20176
TITLE: Evaluation of in vitro antifungal activity of LY121019
AUTHOR(S): Hobbs, M.; Perfect, J.; Durack, D.
CORPORATE SOURCE: Med. Cent., Duke Univ., NC, 27710, USA
SOURCE: European Journal of Clinical Microbiology & Infectious Diseases (1988), 7(1), 77-81
CODEN: *EJCDEU*; ISSN: *0934-9723*
DOCUMENT TYPE: Journal
LANGUAGE: English

AB LY121019 is a new semisynthetic **lipopeptide** antifungal agent with potent in vitro fungicidal activity against multiple clin. strains of **Candida** albicans and C. tropicalis but is 10-100-fold less active against Torulopsis glabrata and C. parapsilosis. Its in vitro activity against C. albicans and C. tropicalis is comparable to that of **amphotericin B** . The in vitro fungicidal activity of this new agent supports further investigations into its use in **treatment** of **Candida** infections.

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO' ENTERED AT 15:08:13 ON 22 OCT 2003)

L27 103 S L24
L28 83 S L25
L29 47 S (L27 OR L28) AND ADMIN?
L30 27 DUP REM L29 (20 DUPLICATES REMOVED)

L30 ANSWER 1 OF 27 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2003475050 IN-PROCESS
DOCUMENT NUMBER: 22913086 PubMed ID: 14550704
TITLE: Echinocandin antifungal drugs.
AUTHOR: Denning David W
CORPORATE SOURCE: Education and Research Centre, Wythenshawe Hospital, Southmoor Road, M23 9LT, Manchester, UK.. ddenning@man.ac.uk
SOURCE: LANCET, (2003 Oct 4) 362 (9390) 1142-51. Journal code: 2985213R. ISSN: 1474-547X.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Abridged Index Medicus Journals; Priority Journals
ENTRY DATE: Entered STN: 20031011
Last Updated on STN: 20031015

AB The echinocandins are large **lipopeptide** molecules that are inhibitors of beta-(1,3)-glucan synthesis, an action that damages fungal cell walls. In vitro and in vivo, the echinocandins are rapidly fungicidal against most **Candida** spp and fungistatic against **Aspergillus** spp. They are not active at clinically relevant concentrations against Zygomycetes, **Cryptococcus** neoformans, or Fusarium spp. No drug target is present in mammalian cells. The first of the class to be licensed was caspofungin, for refractory invasive aspergillosis (about 40% response rate) and the second was micafungin. Adverse events are generally mild, including (for caspofungin) local phlebitis, fever, abnormal liver function tests, and mild haemolysis. Poor absorption after oral **administration** limits use to the intravenous

route. Dosing is once daily and drug interactions are few. The echinocandins are widely distributed in the body, and are metabolised by the liver. Results of studies of caspofungin in candidaemia and invasive candidiasis suggest equivalent efficacy to **amphotericin B**, with substantially fewer toxic effects. Absence of antagonism in combination with other antifungal drugs suggests that combination antifungal **therapy** could become a general feature of the echinocandins, particularly for invasive aspergillosis.

L30 ANSWER 2 OF 27 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2003055660 MEDLINE
DOCUMENT NUMBER: 22452939 PubMed ID: 12565958
TITLE: In vivo characterization of A-192411: a novel fungicidal **lipopeptide** (II).
AUTHOR: Meulbroek Jonathan A; Nilius Angela M; Li Qun; Wang Weibo; Hasvold Lisa; Steiner Beth; Dickman Daniel A; Ding Hong; Frost David; Goldman Robert C; Lartey Paul; Plattner Jacob J; Bennani Youssef L
CORPORATE SOURCE: Infectious Diseases Research, Pharmaceutical Products Division, Abbott Laboratories, Abbott Park, IL 60064, USA.. ybennani@athersys.com
SOURCE: BIOORGANIC AND MEDICINAL CHEMISTRY LETTERS, (2003 Feb 10) 13 (3) 495-7.
Journal code: 9107377. ISSN: 0960-894X.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200308
ENTRY DATE: Entered STN: 20030205
Last Updated on STN: 20030816
Entered Medline: 20030815

AB The ability of the novel antifungal cyclic hexalipopetide A-192411 to **treat** fungal infections in rodents is presented. Efficacy was demonstrated against **Candida** albicans as both prolonged survival of systemically infected mice and clearance of viable yeasts from kidneys. The efficacy of A-192411, **administered** intraperitoneally, was equivalent to amphotercin B at a 4-fold lower dose by weight in the systemic candidiasis models in mice, while the efficacy of A-192441 **administered** intravenously was equivalent to amphotercin B by weight in the **Candida** pyelonephritis model in rats. A-192411 also slightly prolonged the survival of immunocompromised mice infected systemically with **Aspergillus** fumigatus.

L30 ANSWER 3 OF 27 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003337606 EMBASE
TITLE: Antifungal **lipopeptides**: A tale of pseudomycin prodrugs and analogues.
AUTHOR: Chen S.-H.; Rodriguez M.
CORPORATE SOURCE: S.-H. Chen, Lilly Research Laboratories, Division of Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285, United States
SOURCE: Drugs of the Future, (1 May 2003) 28/5 (441-463).
Refs: 106
ISSN: 0377-8282 CODEN: DRFUD4

COUNTRY: Spain
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Systemic fungal infections (SFI) can cause serious life-threatening diseases in normal healthy humans. **Candida** albicans, **Cryptococcus** neoformans and **Aspergillus** fumigatus are the major opportunistic pathogens responsible for SFI. The rising incidence of SFI, especially in immunocompromised patients, attests to the need for more effective **therapies**. Present **treatment** options are limited to three classes of compounds, the polyenes, the azoles and the recently approved **lipopeptide** caspofungin acetate. **Amphotericin B** and azole-based antifungal agents have an inadequate spectrum of activity and rapid emergence of fungal resistance, limited dosage forms and a narrow **therapeutic** window. Several approaches have been taken to address these deficiencies, such as improving the biological and/or toxicology profiles of existing drugs or the search for novel antifungal **lipopeptides**. As a result of this search, several cyclic peptides endowed with promising antifungal activities have been identified, including aureobasidins, echinocandins, papulacandin B and the recently disclosed pseudomycins. The most significant progress on this front was the 2001 launch of caspofungin acetate in the U.S. for the parenteral **treatment** of invasive aspergillosis in patients refractory to or intolerant of other antifungal **therapies**. This review provides a brief update on a number of recently discovered antifungal **lipopeptides**, as well as structural modifications and evaluation of pseudomycin analogues and prodrugs.

L30 ANSWER 4 OF 27 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003286659 EMBASE
TITLE: Anidulafungin.
SOURCE: Drugs in R and D, (2003) 4/3 (167-173).
Refs: 23
ISSN: 1174-5886 CODEN: DRDDFD
COUNTRY: New Zealand
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
039 Pharmacy
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Vicuron Pharmaceuticals (formerly Versicor Inc.) is developing anidulafungin [LY 303366, ECB, V-echinocandin, VEC, VER-02, VER 0021, a **lipopeptide** echinocandin B derivative, for IV **treatment** of mycoses. Anidulafungin acts against fungal infection by inhibiting β-1,3-glucan synthase, an enzyme essential for cell wall formation. Anidulafungin was originally developed for oral use by Eli Lilly and was undergoing phase II clinical trials in the UK and the US for the **treatment** of

Candida, Aspergillus and Pneumocystis **carinii** infections. However, Eli Lilly discontinued development of the oral formulation due to poor oral bioavailability. In May 1999, Versicor obtained exclusive worldwide commercialisation rights to anidulafungin with responsibility for its development and clinical registration. Under the terms of the agreement, Eli Lilly received a signing fee, and will receive milestone payments upon future development of anidulafungin and royalties on future sales. Eli Lilly also retains an option for the development of an oral formulation of the compound. On 3 March 2003, Versicor Inc. of Fremont (California, USA) and Biosearch Italia SpA of Milan (Italy) announced the completion of a merger agreement, whereby Biosearch was merged with and into Versicor in a stock-for-stock exchange valued at $US260.7 million. The combined company temporarily kept the name Versicor until the new name, Vicuron Pharmaceuticals, was announced on 26 March 2003. In January 2003, Versicor announced that positive results from a phase II trial for anidulafungin IV **treatment** involving 120 patients in the US with invasive candidiasis/candidaemia, have led to another double-blind, randomised phase III trial being conducted in the US, Canada and Europe for this indication. This additional phase III trial will enrol approximately 300 patients to investigate the efficacy of IV anidulafungin (200mg loading dose followed by 100mg maintenance dose) versus IV **fluconazole** for 10 to 42 days. Vicuron Pharmaceuticals also plans to seek approval for invasive candidiasis/candidaemia in Europe and Canada in the second half of 2003.

L30 ANSWER 5 OF 27 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2002149950 EMBASE
TITLE: Micafungin sodium (FK-463).
AUTHOR: Fromtling R.A.
CORPORATE SOURCE: Dr. R.A. Fromtling, Regulatory Affairs-International, Merck Research Laboratories, P.O. Box 2000 (RY 33-208), Rahway, NJ 07065-0900, United States. robert_fromtling@merck.com
SOURCE: Drugs of Today, (2002) 38/4 (245-257). Refs: 50 ISSN: 0025-7656 CODEN: MDACAP
COUNTRY: Spain
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 004 Microbiology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB FK-463 (micafungin) represents the latest development candidate in a novel chemical class of echinocandin **lipopeptide** antifungal compounds. This agent has potent in vitro and experimental in vivo activity against a variety of pathogenic **Candida** species (yeasts) and **Aspergillus** fumigatus (filamentous fungus). This compound has favorable pharmacokinetics and a unique mode of action that makes it active against fungal isolates resistant to established antifungal agents, particularly the triazole agent **fluconazole**. Single- and multiple-dose phase I studies in normal human volunteers and phase II clinical trials in patients have been completed, with the compound being

generally well tolerated and efficacious against infections caused by **Candida** and **Aspergillus** species. Published information on the in vitro and experimental in vivo activity, experimental and human pharmacokinetics, and clinical trial data of this new antifungal, echinocandin-like **lipopeptide** are summarized in this monograph. .COPYRGT. 2002 Prous Science. All rights reserved.

L30 ANSWER 6 OF 27 EMBASE COPYRIGHT 2003 ELSEVIER INC. *ALL RIGHTS* RESERVED. on STN DUPLICATE 3

ACCESSION NUMBER: 2003011752 EMBASE
TITLE: Efficacy of micafungin, a new **lipopeptide** antifungal agent, in mouse models of pulmonary aspergillosis.
AUTHOR: Matsumoto S.; Wakai Y.; Watabe E.; Maki K.; Ikeda F.; Tawara S.; Mutoh S.; Matsumoto F.; Kuwahara S.
CORPORATE SOURCE: S. Matsumoto, Medicinal Biology Research Lab., Fujisawa Pharmaceutical Co. Ltd., 2-1-6 Kashima, Yodogawa-ku, Osaka 532-8514, Japan
SOURCE: Japanese Journal of Chemotherapy, (1 Dec 2002) 50/SUPPL. 1 (37-42).
Refs: 15
ISSN: 1340-7007 CODEN: NKRZE5
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
015 Chest Diseases, Thoracic Surgery and Tuberculosis
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English; Chinese

AB The efficacy of micafungin (MCFG), a novel water-soluble **lipopeptide**, was evaluated in mouse models of pulmonary aspergillosis, and compared with that of **amphotericin B** (**AMPH-B**), **fluconazole** (**FLCZ**) and **itraconazole** (**ITCZ**). In pulmonary aspergillosis in mice immunosuppressed by cyclophosphamide, MCFG significantly prolonged the survival of mice infected intranasaly with **Aspergillus** fumigatus at doses of 0.5 and 1 mg/kg (P<0.0125). In mice with pulmonary aspergillosis caused by A. fumigatus, MCFG exhibited 50% effective doses (ED(50)s) in the range of 0.26 to 0.45 mg/kg 15 days after infection, which is comparable to the efficacy of **AMPH-B** (ED(50)S; 0.25 to 0.46 mg/kg), and superior to **FLCZ** and **ITCZ** . The ED(50) of MCFG was comparable to that of **AMPH-B** in mice immunosuppressed by 5-fluorouracil, however, it was 4.1 times inferior to that of **AMPH-B** in mice immunosuppressed by hydrocortisone. When **treatment** with MCFG was initiated 1 day after infection, the ED(50) of MCFG was 1.21 mg/.kg, which was 2.4 times inferior to that of **AMPH-B** and 3.8 times inferior to that of MCFG if initiated 1.5 hours after infection. These results indicate that MCFG may be a potent parenteral **administered** antifungal agent for pulmonary aspergillosis, with efficacy comparable or slightly inferior to that of **AMPH-B**, but superior to that of **FLCZ** and **ITCZ**.

L30 ANSWER 7 OF 27 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS

RESERVED. on STN DUPLICATE 4
ACCESSION NUMBER: 2003011751 EMBASE
TITLE: Efficacy of micafungin, a new **lipopeptide** antifungal agent, in mouse models of disseminated candidiasis and aspergillosis.
AUTHOR: Matsumoto S.; Wakai Y.; Watabe E.; Maki K.; Ikeda F.; Tawara S.; Mutoh S.; Matsumoto F.; Kuwahara S.
CORPORATE SOURCE: S. Matsumoto, Medicinal Biology Research Lab., Fujisawa Pharmaceutical Co. Ltd., 2-1-6 Kashima, Yodogawa-ku, Osaka 532-8514, Japan
SOURCE: Japanese Journal of Chemotherapy, (1 Dec 2002) 50/SUPPL. 1 (30-36).
Refs: 19
ISSN: 1340-7007 CODEN: NKRZE5
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English; Chinese
AB The efficacy of micafungin (MCFG), a novel water-soluble **lipopeptide**, was evaluated in mouse models of disseminated candidiasis and aspergillosis, and was compared with that of **amphotericin B** (**AMPH-B**), **fluconazole** (**FLCZ**) and **itraconazole** (**ITCZ**). In the candidiasis model in mice with granulocytopenia induced by cyclophosphamide, MCFG significantly prolonged the survival of mice infected intravenously with **Candida** albicans at doses of 0.125 mg/kg or higher ($P<0.01$). In candidiasis and aspergillosis caused by C. albicans, **Candida** glabrate, **Candida** tropicalis, **Candida** krusei, **Candida** guilliermondii and **Aspergillus** fumigatus, MCFG exhibited ED(50)s in the range of 0.14-1.61 mg/kg. These data were comparable or inferior to those of **AMPH-B**, but superior to **FLCZ** and **ITCZ**. In disseminated candidiasis in mice immunosuppressed by cyclophosphamide, hydrocortisone or 5-fluorouracil, the ED(50) s of MCFG were 0.14 -0.33mg/kg, superior to **ITCZ** and **FLCZ**, but inferior to **AMPH-B**. In a target organ kidney assay, a single injection of MCFG at a doses of 0.5 or 1.0 mg/kg significantly reduced the yeast viable cell counts in the kidney 24 hours after **treatment** compared to the yeast counts before **treatment**, with an efficacy comparable to **AMPH-B**. These results indicate that MCFG is a potent parenteral **administered therapeutic** agent for disseminated candidiasis and aspergillosis in immunosuppressed mice. The efficacy of MCFG was superior to that of **FLCZ** and **ITCZ**, but comparable or slightly to that of **AMPH-B**.

L30 ANSWER 8 OF 27 MEDLINE on STN DUPLICATE 5
ACCESSION NUMBER: 2002048947 MEDLINE
DOCUMENT NUMBER: 21634458 PubMed ID: 11772269
TITLE: Caspofungin: pharmacology, safety and **therapeutic** potential in superficial and invasive fungal infections.
AUTHOR: Groll A H; Walsh T J
CORPORATE SOURCE: Immunocompromised Host Section, Pediatric Oncology

Branch, National Cancer Institute, National Institutes of Health, Building 10, Rm. 13 N240, 10 Center Drive, Bethesda, MD 20892, USA..
grolla@mail.nih.gov

SOURCE: EXPERT OPINION ON INVESTIGATIONAL DRUGS, (2001 Aug) 10 (8) 1545-58. Ref: 66
Journal code: 9434197. ISSN: 1354-3784.
PUB. COUNTRY: England: United Kingdom
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200203
ENTRY DATE: Entered STN: 20020125
Last Updated on STN: 20020302
Entered Medline: 20020301

AB Invasive fungal infections are important causes of morbidity and mortality in hospitalised patients. Current **therapy** with **amphotericin B** and antifungal triazoles has overlapping targets and is limited by toxicity and resistance. The echinocandin **lipopeptide** caspofungin is the first of a new class of antifungal compounds that inhibit the synthesis of 1,3-beta-D-glucan. This homopolysaccharide is a major component of the cell wall of many pathogenic fungi and yet is absent in mammalian cells. It provides osmotic stability and is important for cell growth and cell division. In vitro, caspofungin has broad-spectrum antifungal activity against **Candida** and **Aspergillus** spp. without cross-resistance to existing agents. The compound exerts prolonged post-antifungal effects and fungicidal activity against **Candida** spp. and causes severe damage of **Aspergillus** fumigatus at the sites of hyphal growth. Animal models have demonstrated efficacy against disseminated candidiasis and disseminated and pulmonary aspergillosis, both in normal and in immunocompromised animals. Caspofungin possesses favourable pharmacokinetic properties and is not metabolised through the cytochrome P450 (CYP) enzyme system. It showed highly promising antifungal efficacy in Phase II and III clinical trials in immunocompromised patients with oesophageal candidiasis. Caspofungin was effective in patients with invasive aspergillosis intolerant or refractory to standard **therapies** . Based on its documented antifungal efficacy and an excellent safety profile, caspofungin has been approved recently by the US Food and Drug **Administration** for the **treatment** of invasive aspergillosis in patients who are refractory to or intolerant of other **therapies** (i.e., **amphotericin B, lipid** formulations of **amphotericin B**, and/or **itraconazole**). Phase III clinical trials in patients with candidaemia and in persistently febrile neutropenic patients requiring empirical antifungal **therapy** are ongoing. This paper reviews the preclinical and clinical pharmacology of caspofungin and its potential role for **treatment** of invasive and superficial fungal infections in patients.

L30 ANSWER 9 OF 27 EMBASE on STN
ACCESSION NUMBER: 2001049796 EMBASE

TITLE: FR131535, a novel water-soluble echinocandin-like **lipopeptide**: Synthesis and biological properties.
AUTHOR: Fujie A.; Iwamoto T.; Sato B.; Muramatsu H.; Kasahara C.; Furuta T.; Hori Y.; Hino M.; Hashimoto S.
CORPORATE SOURCE: A. Fujie, Exploratory Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., 5-2-3 Tokodai, Tsukuba-shi, Ibaraki 300-2698, Japan.
akihiko_fujie@po.fujisawa.co.jp
SOURCE: Bioorganic and Medicinal Chemistry Letters, (12 Feb 2001) 11/3 (399-402).
Refs: 18
ISSN: 0960-894X CODEN: BMCLE8
PUBLISHER IDENT.: S 0960-894X(00)00677-6
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
029 Clinical Biochemistry
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The synthesis and biological properties of a novel water-soluble echinocandin-like **lipopeptide**, FR131535, are described. This compound displayed potent in vitro and in vivo antifungal activities. The hemolytic activity of FR901379 was reduced by replacing the acyl side chain. This compound showed good water-solubility, comparable to the natural product FR901379.

L30 ANSWER 10 OF 27 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 2001-070920 [08] WPIDS
DOC. NO. CPI: C2001-019766
TITLE: Synergistic combination of **lipopeptide** and e.g. azole, polyene, purine nucleotide inhibitor, pyrimidine nucleotide inhibitor, mannan inhibitor or polyoxin is useful for **treating** fungal pathogens.
DERWENT CLASS: B02 C02
INVENTOR(S): IKEDA, F; MATSUMOTO, S; OTOMO, K; WAKAI, Y
PATENT ASSIGNEE(S): (FUJI) FUJISAWA PHARM CO LTD
COUNTRY COUNT: 21
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000072865	A2	20001207	(200108)*	EN	19
RW: AT BE CH CY DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: JP US					
EP 1180038	A2	20020220	(200221)	EN	
R: AT BE CH CY DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE					
JP 2003527314 W		20030916	(200362)		24

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2000072865	A2	WO 2000-JP3340	20000524

EP 1180038	A2	EP 2000-929859	20000524
		WO 2000-JP3340	20000524
JP 2003527314	W	JP 2000-620974	20000524
		WO 2000-JP3340	20000524

FILING DETAILS:

PATENT NO	KIND		PATENT NO
EP 1180038	A2	Based on	WO 2000072865
JP 2003527314	W	Based on	WO 2000072865

PRIORITY APPLN. INFO: AU 1999-663 19990531
AN 2001-070920 [08] WPIDS
AB WO 200072865 A UPAB: 20010207
NOVELTY - A method for **treating** infectious diseases caused by fungi comprises **administration** of a **lipopeptide** (I) in combination with an azole, polyene, purine nucleotide inhibitor, pyrimidine nucleotide inhibitor, mannan inhibitor, protein elongation factor inhibitor, bactericidal/permeability inducing protein product or polyoxin.

DETAILED DESCRIPTION - A method for **treating** infectious diseases caused by fungi comprises **administration** of a **lipopeptide** of formula (I) or a salt in combination with an azole, polyene, purine nucleotide inhibitor, pyrimidine nucleotide inhibitor, mannan inhibitor, protein elongation factor inhibitor, bactericidal/permeability inducing protein product or polyoxin.

R1 = acyl; and

R2, R3 = H or OH

INDEPENDENT CLAIMS are included for (i) a composition for use in the method; (ii) use of **lipopeptides** of formula (I) in the manufacture of a medicament for **treating** fungal diseases.

ACTIVITY - Fungicide.

MECHANISM OF ACTION - Inhibition of cell wall 1,3 beta -D-glucan synthesis.

USE - The method is useful for **treating** fungal diseases, especially caused by **Cryptococcus**, **Candida**, **Aspergillus**, **Histoplasma**, **Coccidioides**, **Paracoccidioides**, Blastomyces, Fusarium, **Sporothrix**, **Trichosporon**, **Rhizopus**, **Pseudallescheria**, **dermatophytes**, **Paeciliomyces**, **Alternaria**, **Curvularia**, **Exophiala**, **Wangiella**, **Penicillium**, **Saccharomyces**, **Dematiaceous** fungi or Pneumocystis **carinii**.

ADVANTAGE - (I) is active against **Candida**, Pneumocystis **carinii** and **Aspergillus** and the combination provides additional options for **treating** **Aspergillus** and other fungal pathogens.

Dwg.0/0

L30 ANSWER 11 OF 27 SCISEARCH COPYRIGHT 2003 THOMSON ISI on STN
ACCESSION NUMBER: 2000:647094 SCISEARCH
THE GENUINE ARTICLE: 345TH
TITLE: Efficacy of the echinocandin caspofungin against disseminated aspergillosis and candidiasis in

cyclophosphamide-induced immunosuppressed mice

AUTHOR: Abruzzo G K (Reprint); Gill C J; Flattery A M; Kong L; Leighton C; Smith J G; Pikounis V B; Bartizal K; Rosen H

CORPORATE SOURCE: MERCK RES LABS, INFECT DIS RY80T 100, POB 2000, RAHWAY, NJ 07065 (Reprint); MERCK RES LABS, VIRUS & CELL BIOL, RAHWAY, NJ 07065; MERCK RES LABS, BIOMETR RES, RAHWAY, NJ 07065; MERCK RES LABS, ANIM HLTH, RAHWAY, NJ 07065

COUNTRY OF AUTHOR: USA

SOURCE: ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (SEP 2000) Vol. 44, No. 9, pp. 2310-2318.
Publisher: AMER SOC MICROBIOLOGY, 1752 N ST NW, WASHINGTON, DC 20036-2904.
ISSN: 0066-4804.

DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE
LANGUAGE: English
REFERENCE COUNT: 24

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB The in vivo efficacy of the echinocandin antifungal caspofungin acetate (caspofungin; MK-0991) was evaluated in models of disseminated aspergillosis and candidiasis in mice with cyclophosphamide (CY)-induced immunosuppression. Caspofungin is a 1,3-beta-D-glucan synthesis inhibitor efficacious against a number of clinically relevant fungi including **Aspergillus** and **Candida** species. Models of CY-induced transient or chronic leukopenia were used with once daily **administration** of **therapy** initiated 24 h after microbial challenge. Caspofungin was effective in **treating** disseminated aspergillosis in mice that were transiently leukopenic (significant prolongation of survival at doses of greater than or equal to 0.125 mg/kg of body weight and a 50% protective dose [PD50] of 0.245 mg/kg/day at 28 days after challenge) or chronically leukopenic (50 to 100% survival at doses of greater than or equal to 0.5 mg/kg and PD(50)s ranging from 0.173 to 0.400 mg/kg/day). Caspofungin was effective in the **treatment** and sterilization of **Candida** infections in mice with transient leukopenia with a 99% effective dose based on reduction in log(10) CFU of **Candida** albicans/gram of kidneys of 0.119 mg/kg and 80 to 100% of the caspofungintreated mice having sterile kidneys at caspofungin doses from 0.25 to 2.0 mg/kg. In **Candida** -infected mice with chronic leukopenia, caspofungin was effective at all dose levels tested (0.25 to 1.0 mg/kg), with the log(10) CFU of C. albicans/gram of kidneys of caspofungin-**treated** mice being significantly lower (>99% reduction) than that of sham-**treated** mice from day 4 to day 28 after challenge. Also, 70 to 100% of the caspofungin-**treated**, chronic leukopenic mice had sterile kidneys at caspofungin doses of 0.5 to 1.0 mg/kg from day 8 to 28 after challenge. Sterilization of **Candida** infections by caspofungin in the absence of host leukocytes provides compelling in vivo evidence for fungicidal activity against C. albicans. Further human clinical trials with caspofungin against serious fungal infections are in progress.

ACCESSION NUMBER: 2000366151 EMBASE

TITLE: FR901469, a novel antifungal antibiotic from an unidentified fungus No.11243. II. In vitro and in vivo activities.
AUTHOR: Fujie A.; Iwamoto T.; Muramatsu H.; Okudaira T.; Sato I.; Furuta T.; Tsurumi Y.; Hori Y.; Hino M.; Hashimoto S.; Okuhara M.
CORPORATE SOURCE: A. Furuta, Department of Parasitology, The Institute of Medical Science, The University of Tokyo, 4-6-1 Shirokanedai, Minato-ku, Tokyo 108-0071, Japan
SOURCE: Journal of Antibiotics, (2000) 53/9 (920-927).
Refs: 25
ISSN: 0021-8820 CODEN: JANTAJ
COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB FR901469 is a water-soluble macrocyclic lipopeptidolactone (C71H116N14O23) that has inhibitory activity against 1,3β-glucan synthase and exhibits in vitro and in vivo antifungal activity against both **Candida** albicans and **Aspergillus** fumigatus. The MICs of FR901469 against **Candida** albicans FP633 and **Aspergillus** fumigatus FP1305 in a micro-broth dilution test were 0.63 and 0.16 μg/ml, respectively. FR901469 showed excellent efficacy by subcutaneous injection against both **Candida** albicans and **Aspergillus** fumigatus in a murine systemic infection mode, with ED50s of 0.32 and 0.2 mg/kg, respectively. This compound also showed potent anti-Pneumocystis activity in the nude mice model with experimental Pneumocystis pneumonia. The hemolytic activity of FR901469 towards mouse red blood cells is about 30-fold weaker than that of **amphotericin B**.

L30 ANSWER 13 OF 27 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2000145379 MEDLINE
DOCUMENT NUMBER: 20145379 PubMed ID: 10681328
TITLE: Efficacy of FK463, a new **lipopeptide** antifungal agent, in mouse models of pulmonary aspergillosis.
AUTHOR: Matsumoto S; Wakai Y; Nakai T; Hatano K; Ushitani T; Ikeda F; Tawara S; Goto T; Matsumoto F; Kuwahara S
CORPORATE SOURCE: Medicinal Biology Research Laboratories, Fujisawa Pharmaceutical Co., Ltd., Kashima, Yodogawa-ku, Osaka 532-8514, Japan.
SOURCE: ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (2000 Mar) 44 (3) 619-21.
Journal code: 0315061. ISSN: 0066-4804.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000413
Last Updated on STN: 20000413
Entered Medline: 20000403
AB The efficacy of FK463, a novel water-soluble **lipopeptide**,

was evaluated in mouse models of pulmonary aspergillosis and was compared with that of **amphotericin B** (**AMPH-B**). In the pulmonary aspergillosis models induced by intranasal inoculation, FK463 exhibited good efficacy, with 50% effective doses in the range of 0. 26 to 0.51 mg/kg of body weight; these values were comparable to those of **AMPH-B**. In an **Aspergillus** target organ assay with immunosuppressed mice, under conditions of constant plasma levels of FK463, using a subcutaneously implanted osmotic pressure pump, a significant reduction in viable fungal cells was observed at plasma FK463 levels of 0.55 to 0.80 microgram/ml or higher. We conclude that FK463 is highly effective in the **treatment** of pulmonary aspergillosis in this animal model. These results indicate that FK463 may be a potent parenterally **administered** antifungal agent for pulmonary aspergillosis.

L30 ANSWER 14 OF 27 MEDLINE on STN DUPLICATE 7
ACCESSION NUMBER: 2000145378 MEDLINE
DOCUMENT NUMBER: 20145378 PubMed ID: 10681327
TITLE: Efficacy of FK463, a new **lipopeptide** antifungal agent, in mouse models of disseminated candidiasis and aspergillosis.
AUTHOR: Ikeda F; Wakai Y; Matsumoto S; Maki K; Watabe E; Tawara S; Goto T; Watanabe Y; Matsumoto F; Kuwahara S
CORPORATE SOURCE: Medicinal Biology Research Laboratories, Japan.. fumiaki_ikeda@po.fujisawa.co.jp
SOURCE: ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (2000 Mar) 44 (3) 614-8.
Journal code: 0315061. ISSN: 0066-4804.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200004
ENTRY DATE: Entered STN: 20000413
Last Updated on STN: 20000413
Entered Medline: 20000403

AB The efficacy of intravenous injection of FK463, a novel water-soluble **lipopeptide**, was evaluated in mouse models of disseminated candidiasis and aspergillosis and was compared with those of **fluconazole** (**FLCZ**) and **amphotericin B** (**AMPH-B**). In the candidiasis model, FK463 significantly prolonged the survival of intravenously infected mice at doses of 0.125 mg/kg of body weight or higher. In disseminated candidiasis caused by **Candida** species, including **FLCZ**-resistant **Candida** albicans, FK463 exhibited an efficacy 1.4 to 18 times inferior to that of **AMPH-B**, with 50% effective doses (ED(50)s) ranging from 0.21 to 1.00 mg/kg and 0.06 to 0.26 mg/kg, respectively, and was much more active than **FLCZ**. The protective effect of FK463 was not obviously influenced by the fungal inoculum size, the starting time of the **treatment**, or the immunosuppressed status of the host. The reduction in efficacy was less than that observed with **FLCZ** or **AMPH-B**. The efficacy of FK463 was also evaluated in the disseminated candidiasis target organ assay and was compared with those of **FLCZ** and **AMPH-B**.
Efficacies were evaluated on the basis of a comparison between the

mean log(10) CFU in kidneys in the groups **treated** with antifungal agents and that in control group. A single dose of FK463 at 0.5 mg/kg or higher significantly reduced the viable counts in kidneys compared with the numbers of yeast cells before **treatment**, and its efficacy was comparable to that of **AMPH-B**, while **FLCZ** at 4 mg/kg showed only a suppressive effect on the growth of C. albicans in the kidneys. In the disseminated aspergillosis model, FK463 given at doses of 0.5 mg/kg or higher significantly prolonged the survival of mice infected intravenously with **Aspergillus** fumigatus conidia. The efficacy of FK463 was about 2 times inferior to that of **AMPH-B**, with ED(50)s ranging from 0.25 to 0.50 mg/kg and 0.11 to 0.29 mg/kg, respectively. These results indicate that FK463 may be a potent parenterally **administered therapeutic** agent for disseminated candidiasis and aspergillosis.

L30 ANSWER 15 OF 27 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 1999110917 EMBASE
TITLE: Current approaches to diagnosis and **treatment** of fungal infections in children infected with human immuno deficiency virus.
AUTHOR: Muller F.-M.C.; Groll A.H.; Walsh T.J.
CORPORATE SOURCE: F.-M.C. Muller, Inst. Molekulare Infektionsbiologie, Universitat Wurzburg, Rontgenring 11, D-97070 Wurzburg, Germany. fmmueller@mail.uni-wuerzburg.de
SOURCE: European Journal of Pediatrics, (1999) 158/3 (187-199).
Refs: 111
ISSN: 0340-6199 CODEN: EJPEDT
COUNTRY: Germany
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 007 Pediatrics and Pediatric Surgery
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The prolonged survival of profoundly immunocompromised patients has revealed mucosal and invasive fungal infections to be major causes of morbidity and mortality in advanced HIV disease in children of all age groups. Antifungal resistance has become a clinically relevant problem. Paediatricians caring for HIV-infected children need to be aware of these increasingly frequent and often life-threatening infectious complications. This article reviews what is currently known about epidemiology, clinical presentation, diagnosis and **treatment** of mucosal and invasive fungal infections in children and adolescents with HIV disease. **Candida** spp. have become a leading bloodstream isolate in hospitalised patients; mucosal candidiasis is the most prevalent opportunistic infection in HIV-infected patients, and in both invasive and superficial infections, non **Candida** albicans spp. are on the increase. Invasive pulmonary aspergillosis has surfaced as an HIV-associated complication and previously uncommon fungi are more frequently encountered. HIV-infected individuals are particularly susceptible to Peumocystis **carinii**, **Cryptococcus** neoformans and infections by endemic fungi, such as **Histoplasma** capsulatum, **Coccidioides** immitis, **Penicillium** marneffei, and others. Newer

immunological and molecular-based methods provide early and rapid diagnosis and monitoring. Potent and broad- spectrum third generation triazoles and novel fungicidal **lipopeptides** of the echinocandin class of antifungal antibiotics have entered clinical trials. Immunmodulation by recombinant cytokines and antifungal vaccines are very actively pursued inroads to adjunctive and **preventive** immunotherapy. Conclusion Mucosal and invasive fungal refections will remain important complications in HIV-infected children of all age groups. Interventional studies and well documented case series are needed to improve the molecular diagnosis, **treatment** and **prevention** of invasive fungal infections in the paediatric HIV-infected population.

L30 ANSWER 16 OF 27 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 1998-322454 [28] WPIDS
DOC. NO. CPI: C1998-099177
TITLE: New antifungal **lipopeptide**(s) from Pseudomonas viridiflava - used as antimycotics in human and veterinary medicine or as plant protection agents.
DERWENT CLASS: B04 C03 C05 D16
INVENTOR(S): MARTINEZ-MILLER, C; MILLER, R V; STROBEL, G A; STROEBEL, G A
PATENT ASSIGNEE(S): (PHAR-N) PHARMAGENESIS INC
COUNTRY COUNT: 22
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 9823281	A1	19980604	(199828)*	EN	59
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE					
W: AU CA CN JP					
AU 9874087	A	19980622	(199844)		
US 6103875	A	20000815	(200041)		

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 9823281	A1		WO 1997-US21543	19971126
AU 9874087	A		AU 1998-74087	19971126
US 6103875	A	Provisional	US 1996-32037P	19961126
		Provisional	US 1997-41762P	19970331
			US 1997-978788	19971126

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 9874087	A	Based on	WO 9823281

PRIORITY APPLN. INFO: US 1997-41762P 19970331; US 1996-32037P 19961126; US 1997-978788 19971126
AN 1998-322454 [28] WPIDS
AB WO 9823281 A UPAB: 19980715
Purified **lipopeptide** (I) produced by Pseudomonas viridiflava (P. v.) is characterised by its ability to inhibit **Candida** albicans.

Also new are: (1) acyl derivatives (Ia) of (I), especially (I) of 1137, 1153, 1164 or 1181 Da, characterised by: (a) a clogP value of greater than about 3.5 (a measure of log P for the whole molecule, log P = octanol-water partition coefficient); and (b) an ability to inhibit growth of **Candida** albicans to an extent which is substantially the same or improved compared to the non-derivatised peptide; and (2) strains of P. v. that produce (I) which are characterised by: (a) fluorescence on King's B medium; (b) an inability to produce acid from sucrose; (c) an absence of oxidase and arginine dihydrolase activities; (d) an absence of levan formation in a levan test; (e) a positive potato rot test; and (f) a positive hypersensitivity in tobacco.

USE - (I), designated ecomycins, are useful as antifungal agents (used as whole broth, supernatant or extract). (I) can be used for **treating** or **preventing** infections by C. albicans, C. glabrata, C. parasilopsis or **Cryptococcus** neoformans; or to protect plants against e.g. **Alternaria** solani, Fusarium species, Rhizoctonia solani, Sclerotinia sclerotioria etc. They may also be used (not claimed) to protect industrial materials such as wood, jet fuel, cosmetics and paints. Also (I) can be used as a synergist for **amphotericin B** (AB), and then allows the dose of AB required for a **therapeutic** effect to be reduced by at least 30% (thus reducing AB-associated side effects). (I) are **administered** orally, topically or intravenously, typically at 5-20 mg/kg/day, together with 0.2-0.3 mg/kg/day AB. No specific peptide sequence or formula for (I) is given in the specification.

ADVANTAGE - (I) have good solubility in water and other solvents; are relatively stable under alkaline conditions; stable for several days at 4-60 deg. C, and have relatively low toxicity. Dwg.0/8

L30 ANSWER 17 OF 27 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER:	97243231 EMBASE
DOCUMENT NUMBER:	1997243231
TITLE:	**Lipopeptide** antifungal agents: Amine conjugates of the semi-synthetic pneumocandins L-731,373 and L-733,560.
AUTHOR:	Zambias R.A.; James C.; Abruzzo G.K.; Bartizal K.F.; Hajdu R.; Thompson R.; Nollstadt K.H.; Marrinan J.; Balkovec J.M.
CORPORATE SOURCE:	J.M. Balkovec, Department of Medicinal Chemistry, Merck Research Laboratories, P.O. Box 2000, Rahway, NJ 07065-0900, United States
SOURCE:	Bioorganic and Medicinal Chemistry Letters, (1997) 7/15 (2021-2026). Refs: 10 ISSN: 0960-894X CODEN: BMCLE8
PUBLISHER IDENT.:	S 0960-894X(97)00359-4
COUNTRY:	United Kingdom
DOCUMENT TYPE:	Journal; Article
FILE SEGMENT:	004 Microbiology 030 Pharmacology 037 Drug Literature Index
LANGUAGE:	English
SUMMARY LANGUAGE:	English

AB Amine conjugates of the semi-synthetic 1,3-β-(D)-glucan

synthesis inhibitors L-731,373 (3) and L-733,560 (4) were prepared and evaluated for in vitro and in vivo antifungal activity. Tricationic analogs were more potent than the dicationic which were more potent than the monocationic. The L-ornithine conjugate of 4 possessed excellent pharmacokinetic parameters but lacked sufficient antifungal spectrum for development.

L30 ANSWER 18 OF 27 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 96400672 MEDLINE
DOCUMENT NUMBER: 96400672 PubMed ID: 8807048
TITLE: New model of oropharyngeal and gastrointestinal colonization by **Candida** albicans in CD4+ T-cell-deficient mice for evaluation of antifungal agents.
AUTHOR: Flattery A M; Abruzzo G K; Gill C J; Smith J G; Bartizal K
CORPORATE SOURCE: Antibiotic Discovery and Development, Merck Research Laboratories, Rahway, New Jersey 07065-0900, USA.
SOURCE: ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1996 Jul) 40 (7) 1604-9.
Journal code: 0315061. ISSN: 0066-4804.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; AIDS
ENTRY MONTH: 199611
ENTRY DATE: Entered STN: 19961219
Last Updated on STN: 19961219
Entered Medline: 19961122

AB A new model for the evaluation of antifungal compounds against oropharyngeal and gastrointestinal mucosal colonization by **Candida** albicans was developed. To simulate the immune deficiency observed in AIDS patients, mice were depleted of CD4+ T lymphocytes by the injection of either GK1.5 hybridoma cells or purified anti-CD4+ T lymphocytes by the injection of either GK1.5 hybridoma cells or purified anti-CD4+ monoclonal antibody derived from GK1.5 hybridoma cells in tissue culture. Fluorescence-activated cell sorter analysis of splenic lymphocytes confirmed the elimination of the CD4+ T-cell population. Gentamicin, a broad-spectrum, nonabsorbable aminoglycoside antibiotic, was given via the drinking water to reduce the normal gastrointestinal microflora, allowing less competition for colonization of the gastrointestinal tract by the C. albicans isolates. Mice were challenged by gavage and swabbing their oral mucosae with a pure culture of C. albicans. Gentamicin was withdrawn 3 days postchallenge, and antifungal compounds were **administered** via the drinking water ad libitum at concentrations ranging from 25 to 400 micrograms/ml. L-693989, a water-soluble phosphorylated cyclic **lipopeptide** prodrug of pneumocandin Bo, and L-733560, a semisynthetic derivative of pneumocandin Bo, are inhibitors of 1,3-beta-D-glucan synthesis that exhibit potent in vivo anti-**Candida** spp. and anti-Pneumocystis **carinii** activities. The efficacies of L-693989, L-733560, **fluconazole**, **ketoconazole**, and **nystatin** were evaluated in this new oropharyngeal and gastrointestinal model of mucosal colonization. L-693989, L-733560, **fluconazole**, and **ketoconazole** showed superior efficacies in reducing the numbers of C. albicans CFU per gram of feces and the numbers of

oral CFU relative to those in sham-**treated** controls in this model, while **nystatin** was moderately effective in reducing oral and fecal colonization by C. albicans in this model.

L30 ANSWER 19 OF 27 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 96169300 EMBASE
DOCUMENT NUMBER: 1996169300
TITLE: Do interactions with phospholipids contribute to the prolonged retention of polypeptides within the lung?.
AUTHOR: McAllister S.M.; Alpar H.O.; Teitelbaum Z.; Bennett D.B.
CORPORATE SOURCE: Roche Bioscience, 3401 Hillview Drive,Palo Alto, CA 94304, United States
SOURCE: Advanced Drug Delivery Reviews, (1996) 19/1 (89-110). ISSN: 0169-409X CODEN: ADDREP
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 030 Pharmacology
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Several amphipathic or hydrophobic polypeptides exhibited prolonged retention in the lung following pulmonary **administrations.** The physicochemical basis for prolonged retention remains uncertain but may be related to hydrophobic and electrostatic interactions between the polypeptides and the phospholipids of lung tissues. The pulmonary absorption characteristics of detirelix, polymyxin B, and cyclosporin A were reviewed in relation to their interactions with phospholipids. Phospholipid interactions were evaluated qualitatively by comparison of the efficiencies of polypeptides' incorporation into **liposomes**, and by a quantitative comparison of the polypeptide affinities for immobilized artificial membranes (IAM). Detirelix and cyclosporin A exhibited prolonged pulmonary retention compared with polymyxin B. Those observations correlated with the polypeptides' **liposomal** incorporation efficiencies and IAM affinities. The duration of absorption of all three polypeptides was further extended following pulmonary **administration** of their **liposomal** formulations. A fourth polypeptide, **lipopeptide** L-693,989, was identified as possessing the structural hydrophobicity sufficient to interact strongly with phospholipid bilayers: a possible explanation for its prolonged pulmonary retention.

L30 ANSWER 20 OF 27 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 94371795 EMBASE
DOCUMENT NUMBER: 1994371795
TITLE: Increased antifungal activity of L-733,560, a water-soluble, semisynthetic pneumocandin, is due to enhanced inhibition of cell wall synthesis.
AUTHOR: Kurtz M.B.; Douglas C.; Marrinan J.; Nollstadt K.; Onishi J.; Dreikorn S.; Milligan J.; Mandala S.; Thompson J.; Balkovec J.M.; Bouffard F.A.; Dropinski J.F.; Hammond M.L.; Zambias R.A.; Abruzzo G.; Bartizal K.; McManus O.B.; Garcia M.L.
CORPORATE SOURCE: Dept. of Infectious Disease Research, Merck Research

Laboratories, P.O. Box 2000,Rahway, NJ 07065-0900, United States
SOURCE: Antimicrobial Agents and Chemotherapy, (1994) 38/12 (2750-2757).
ISSN: 0066-4804 CODEN: AMACCQ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB The pneumocandins are natural **lipopeptide** products of the echinocandin class which inhibit the synthesis of 1,3-β-D-glucan in susceptible fungi. The lack of a corresponding pathway in mammalian hosts makes this mode of action an attractive one for **treating** systemic infections. Substitution by an aminoethyl ether at the hemiaminal and dehydration and reduction of the glutamine of pneumocandin B0 produced a semisynthetic compound (L-733,560) with intrinsic water solubility, significantly increased potency, and a broader antifungal spectrum. To evaluate the mechanism for the improved antifungal efficacy, we determined that L-733,560 was a more potent inhibitor of glucan synthase activity in vitro, did not affect the other membrane- bound enzymes tested, conferred susceptibility to lysis in the absence of osmotic support, and did not disrupt currents in **liposomal** bilayers or 86Rb+ fluxes from **liposomes**. In **Aspergillus** species L-733,560 also produced the same morphological alterations as pneumocandin B0. A stereoisomer of L-733,560 with poor antifungal activity was a weak inhibitor of glucan synthase. All of these results support the notion that the enhanced antifungal activity of L-733,560 is achieved by superior inhibition of glucan synthesis and not by nonspecific membrane effects or a second mode of action.

L30 ANSWER 21 OF 27 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 93263640 MEDLINE
DOCUMENT NUMBER: 93263640 PubMed ID: 8494367
TITLE: Comparative efficacies of cilofungin (Ly121019) and **amphotericin B** against disseminated **Candida** albicans infection in normal and granulocytopenic mice.
AUTHOR: Khardori N; Nguyen H; Stephens L C; Kalvakuntla L; Rosenbaum B; Bodey G P
CORPORATE SOURCE: Department of Medical Specialities, University of Texas M.D. Anderson Cancer Center, Houston 77030, USA.
SOURCE: ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1993 Apr) 37 (4) 729-36.
Journal code: 0315061. ISSN: 0066-4804.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199306
ENTRY DATE: Entered STN: 19930625
Last Updated on STN: 19930625
Entered Medline: 19930611

AB The efficacies of cilofungin (Ly121019), a semisynthetic **lipopeptide** antifungal agent, and **amphotericin B** in the **treatment** of disseminated candidiasis in normal and neutropenic mice were compared. In mice infected with 2 x 10(6) CFU of **Candida** albicans, **treatment** with cilofungin in twice-daily doses of 25 or 35 mg/kg of body weight by intraperitoneal injection for 10 days gave survival rates of 83 and 90%. In contrast, there was 97% mortality in infected controls receiving 2 x 10(6) CFU intravenously and 93% survival in mice **treated** with 1 mg of **amphotericin B** per kg once a day. Mice rendered granulocytopenic by the **administration** of cyclophosphamide showed survival rates of 83 and 80% when **treated** with 25 or 35 mg of cilofungin per kg for 10 days compared with 43% survival rate in mice **treated** with 1 mg of **amphotericin B** per kg ($P = 0.0030$ and $P = 0.0080$, respectively). Similar results were obtained when the two antifungal agents were **administered** for a period of 30 days. **Administration** of 25 or 35 mg of cilofungin per kg twice a day to granulocytopenic mice receiving 10(6) CFU of C. albicans gave survival rates of 93% and 93% compared with 53% survival with **amphotericin B**. With 15 mg of cilofungin per kg twice a day for 10 days, a survival rate of 43 to 50% was observed in both normal and granulocytopenic mice compared with 56 and 60%, respectively, when this dosage was continued for 30 days. Cilofungin eradicated C. albicans from the kidneys, spleens, and livers of surviving animals. No toxic effects were observed with any of the dosage regimens used. The clearance of C. albicans from the kidneys, spleens, livers, and brains in normal mice was studied following infection with 5 x 10(5) and 1 x 10(5) intravenously. The mice in the **treatment** groups received 25 mg of cilofungin per kg twice a day for 10 days. In 8 to 12 days, this **treatment** was able to clear the organisms from the kidneys, spleens, and livers of mice infected with 5 x 10(5) C. albicans. Mice infected with 10(5) C. albicans and **treated** with cilofungin (25 mg/kg) twice a day for 10 days had no organisms in the kidney, spleen, and liver at days 8, 2, and 8, respectively. There was 1-log-unit reduction in C. albicans counts in brain tissue from mice of one of the **treated** groups between 2 h and 2 days postinfection, after which the numbers of organisms remained the same until day 12. These data demonstrate the efficacy of cilofungin in the **treatment** of disseminated C. albicans infections in normal and granulocytopenic mice. The **treatment** regimen used in this study was able to clear C. albicans from the kidneys, spleen, and liver but not from brain tissue.

L30 ANSWER 22 OF 27 EMBASE COPYRIGHT 2003 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 93101096 EMBASE
DOCUMENT NUMBER: 1993101096
TITLE: Correlation of cilofungin in vivo efficacy with its activity against **Aspergillus** fumigatus (1,3)-β-D-glucan synthase.
AUTHOR: Beaulieu D.; Tang J.; Zeckner D.J.; Parr Jr. T.R.
CORPORATE SOURCE: Bristol-Myers Squibb, Pharmaceutical Research Institute, Microbiology Department (104), 5 Research Parkway,Wallingford, CT 06492, United States
SOURCE: FEMS Microbiology Letters, (1993) 108/2 (133-137).

ISSN: 0378-1097 CODEN: FMLED7
COUNTRY: Netherlands
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB (1,3)-β-D-Glucan synthase is a cell wall synthesis enzyme that is the target of cilofungin, an antifungal agent of the **lipopeptide** class. Cilofungin's glucan synthase inhibitory activity, MIC, and effective dose 50% in a systemic infection mouse model tend to correlate for **Candida** albicans. This correlation is not seen in **Aspergillus** fumigatus, MICs for cilofungin against A. fumigatus were consistently > 125 μg/ml while the effective dose 50% in a systemic aspergillosis model was determined to be 20.6 mg/kg. To begin to understand this discrepancy, we examined the A. fumigatus glucan synthase. This cell wall enzyme was prepared and its activity was measured by [14C]-glucose incorporation from UDP-[U-14C]glucose into an acid insoluble polymer formed in the presence of α-amylase. Enzyme activity in crude membrane preparations was measured in the presence of several antifungal agents. Enzyme inhibition results showed that 1 μg/ml of papulacandin B, echinochandin B, aculeacin A and cilofungin all inhibited A. fumigatus glucan synthase activity (40-71%) while 1 μg/ml of **amphotericin B**, **fluconazole**, **ketoconazole** and nikkomycin did not affect enzyme activity. A correlation was therefore established between the inhibitory effect of cilofungin on the A. fumigatus glucan synthase and the effective dose 50% obtained in a systemic aspergillosis mouse model.

L30 ANSWER 23 OF 27 EMBASE on STN DUPLICATE 10
ACCESSION NUMBER: 92249284 EMBASE
DOCUMENT NUMBER: 1992249284
TITLE: In vitro antifungal activities and in vivo efficacies of 1,3-β-D-glucan synthesis inhibitors L-671,329, L-646,991, tetrahydroechinocandin B, and L- 687,781, a papulacandin.
AUTHOR: Bartizal K.; Abruzzo G.; Trainor C.; Krupa D.; Nollstadt K.; Schmatz D.; Schwartz R.; Hammond M.; Balkovec J.; Vanmiddlesworth F.
CORPORATE SOURCE: Merck and Co., Inc.,Rahway, NJ 07065, United States
SOURCE: Antimicrobial Agents and Chemotherapy, (1992) 36/8 (1648-1657).
ISSN: 0066-4804 CODEN: AMACCQ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The in vivo anti-**Candida** activities of 1,3-β-D-glucan synthesis inhibitors L-671,329, L-646,991 (cilofungin), L-687,901 (tetrahydroechinocandin B), and L-687,781 (a papulacandin analog) were evaluated by utilizing a murine model of disseminated candidiasis that has enhanced susceptibility to **Candida**

albicans but increased sensitivity for discriminating antifungal efficacy. DBA/2 mice were challenged intravenously with 1 x 104 to 5 x 104 CFU of C. albicans MY1055 per mouse. Compounds were **administered** intraperitoneally at concentrations ranging from 1.25 to 10 mg/kg of body weight twice daily for 4 days. At 6 h and 1, 2, 3, 4, 7, and 9 days after challenge, five mice per group were sacrificed and their kidneys were homogenized and plated for enumeration of **Candida** organisms (CFU per gram). Progressiveness of response trends and no-statistical-significance-of- trend doses were derived to rank compound efficacy. 1,3-β-D-Glucan synthesis 50% inhibitory concentrations were determined by using a C. albicans (MY1208) membrane glucan assay. **Candida** and **Cryptococcus** neoformans MICs and minimal fungicidal concentrations were determined by broth microdilution. L-671,329, L-646,991, L-687,901, and L-687,781 showed similar 1,3-β-D-glucan activities, with 50% inhibitory concentrations of 0.64, 1.30, 0.85, and 0.16 μg/ml, respectively. Data from in vitro antifungal susceptibility studies showed that L-671,329, L-646,991, and L-687,901 had similar MICs ranging from 0.5 to 1.0 μg/ml, while L-687,781 showed slightly higher MICs of 1.0 to 2.0 μg/ml for C. albicans MY1055. **Lipopeptide** compounds were ineffective against C. neoformans strains. Results from in vivo experiments comparing significant trend and progressiveness in response analyses indicated that L-671,329 and L-646,991 were equipotent but slightly less active than L-687,901, while L- 687,781 was ineffective at 10 mg/kg. Fungicidal activities of L-671,329, L- 646,991, and L-687,901 were observed in vivo, with significant reduction in **Candida** CFU per gram of kidneys compared with those in sham-**treated** mice at doses of ≥2.5 mg/kg evident as early as 1 day after challenge.

L30 ANSWER 24 OF 27 WPIDS COPYRIGHT 2003 THOMSON DERWENT on STN
ACCESSION NUMBER: 1991-283330 [39] WPIDS
DOC. NO. CPI: C1991-122707
TITLE: New antibiotic cyclic **lipo-peptide** - has antifungal activity against e.g. **Candida** albicans and Pneumocystis **carinii**.
DERWENT CLASS: B02 C02 D16
INVENTOR(S): FOUNTOULA, J M; KAPLAN, L; LIESCH, J M; MASUREKAR, P S; SESIN, D F; WICHMANN, C F; FOUNTOULAKIS, J M
PATENT ASSIGNEE(S): (MERI) MERCK & CO INC
COUNTRY COUNT: 10
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
EP 448355	A	19910925	(199139)*		
R: CH DE FR GB IT LI NL					
US 5049546	A	19910917	(199140)		
CA 2038532	A	19910920	(199149)		
JP 04217683	A	19920807	(199238)		12
US 5162211	A	19921110	(199248)		9
EP 448355	A3	19920624	(199333)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE

EP 448355	A		EP 1991-302373	19910319
US 5049546	A		US 1990-495653	19900319
JP 04217683	A		JP 1991-54787	19910319
US 5162211	A	Div ex	US 1990-495653	19900319
			US 1991-662084	19910228
EP 448355	A3		EP 1991-302373	19910319

FILING DETAILS:

PATENT NO	KIND		PATENT NO
US 5162211	A	Div ex	US 5049546

PRIORITY APPLN. INFO: US 1990-495653 19900319
AN 1991-283330 [39] WPIDS
AB EP 448355 A UPAB: 19931119
A cyclic pipopeptide of formula (I) is new. A method of producing (I) by cultivating Zalerion arboricola ATCC 20958 in a medium of C, N and inorganic salts under aerobic conditions is claimed.

USE/ADVANTAGE - (I) has antifungal properties against both filamentous fungi and yeast, esp against organisms which cause mycotic infections such as **candida** albicans, **Candida** rugosa and **Candida** parapsilosis. (I) is also useful for **treating** Pneumocystis **carinii** the causative agent of pneumonia which is partic severe to immune compromised patients such as those suffering from AIDS. Unlike certain other antifungal agents such as **amphotericin B**, (I) has low side effects. (I) is also able to **prevent** blood lysis which is a potentially fatal side reaction associated with known cpds.

Admin is oral, rectal, topical, parenteral, pulmonary, nasal or by insufflation. Compsns contain at least 1 wt% of (I).

In an example Pneumocystis **carinii** pneumonia was induced in Sprague-Dawley rats. The rats were then **treated** with (I) which had good antipneumocystis activity giving an ED90 of at least 1.0 mg/kg. @(16pp Dwg.No.0/1)@
0/1
ABEQ US 5049546 A UPAB: 19930928
New cyclic **lipopeptide** has the formula (I).

USE - Cpd. (I) is useful in the **treatment** or **prevention** of Pneumocystis **carinii** infections in mammals.
ABEQ US 5162211 A UPAB: 19930928
Prodn. of a cyclic **lipopeptide** of formula (I) comprises aerobic culture of Zalerion arboricola ATCC 20958 in a nutrient medium contg. assimilable C and N sources and inorganic salts. (I) is extracted, cored, and purified by chromatography.

USE/ADVANTAGE - Used as an antifungal agent vs. organisms which cause pathogenic mycotic infections, e.g, **Candida** albicans, **Candida** nigosa and **Candida** parapsilosis.
0/1

L30 ANSWER 25 OF 27 MEDLINE on STN
ACCESSION NUMBER: 92007924 MEDLINE
DOCUMENT NUMBER: 92007924 PubMed ID: 1655435

TITLE: In vitro comparison of cilofungin alone and in combination with other antifungal agents against clinical isolates of **Candida** species.
AUTHOR: Smith K R; Lank K M; Dismukes W E; Cobbs C G
CORPORATE SOURCE: Department of Medicine, University of Alabama, Birmingham 35294.
SOURCE: EUROPEAN JOURNAL OF CLINICAL MICROBIOLOGY AND INFECTIOUS DISEASES, (1991 Jul) 10 (7) 588-92. Journal code: 8804297. ISSN: 0934-9723.
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199111
ENTRY DATE: Entered STN: 19920124
Last Updated on STN: 19920124
Entered Medline: 19911114

AB Cilofungin, a **lipopeptide** antifungal agent, was tested for in vitro activity alone and in combination with **ketoconazole**, **itraconazole**, **flucytosine** and **amphotericin B** against 102 clinical isolates of **Candida** species. At 48 hours all isolates of **Candida** albicans, **Candida** tropicalis, **Candida** paratropicalis and **Candida** glabrata were inhibited by less than or equal to 5 meg/ml of cilofungin. In contrast, the MIC90 for **Candida** krusei was 10 mcg/ml and for **Candida** parapsilosis greater than 40 mcg/ml. The interaction of combinations of cilofungin with **amphotericin B**, **itraconazole**, **ketoconazole** and **flucytosine** was additive or indifferent at 48 hours for 100%, 88%, 78% and 70% of all **Candida** species isolates, respectively. Overall, cilofungin demonstrated good activity in vitro against most **Candida** species isolates.

L30 ANSWER 26 OF 27 EMBASE on STN
ACCESSION NUMBER: 90142736 EMBASE
DOCUMENT NUMBER: 1990142736
TITLE: Comparative effects of cilofungin and **amphotericin B** on experimental murine candidiasis.
SOURCE: Antimicrobial Agents and Chemotherapy, (1990) 34/5 (746-750).
ISSN: 0066-4804 CODEN: AMACCQ
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 004 Microbiology
030 Pharmacology
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English

AB The effectiveness of cilofungin (LY121019, referred to hereafter as LY), a **lipopeptide**, was studied in a murine candidiasis model. CD-1 mice (5 weeks old) were injected intravenously with 3 x 105 **Candida** albicans yeast cells. Intraperitoneal LY or **amphotericin B** (**AmB**) **therapy** was begun 4 days after infection and was continued daily for 2 weeks. LY and **AmB** were compared at 62.5, 6.25 and 0.625

mg/kg per day, with the LY dose split into two **treatments** per day. Mice were observed for 30 days postinfection, and survivors were necropsied. **AmB** at 62.5 mg/kg per day was lethal in the absence of infection. Cumulative mortality for infected controls was 94% (17 of 18). Survival of mice **treated** with the control diluent for LY was the same as survival with no **treatment**. Survival after 0.625 mg of LY per kg per day was the same as that of the controls, and 6.25 or 62.5 mg of LY per kg per day was significantly superior. **AmB treatment** at 0.625 or 6.25 mg/kg per day was protective and superior to the same LY doses. Atrophied kidneys were common in **AmB-treated** mice, and mice **treated** with 6.25 mg of **AmB** per kg per day appeared ill during **therapy**. The number of CFU recovered from kidneys and spleens of surviving mice reflected the same relationships between drugs and doses as those described for mortality. C. albicans was not cleared from the kidneys of mice in any group, and only in the 6.25-mg/kg-per-day **AmB treatment** group was no detectable C. albicans found in the spleens. These data indicate that LY or **AmB** suppresses **candida** infection but neither is curative in this model.

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